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(54) Title: NOVEL ISOXAZOLINE AND ISOXAZOLE FIBRINOLYSIN RECEPTOR ANTAGONISTS

(57) Abstract

This invention relates to novel isoxazolines and isoxazoles which are useful as antagonists of the platelet glycoprotein IIb/IIIa fibrinogen receptor complex, to pharmaceutical compositions containing such compounds, processes for preparing such compounds, and to methods of using these compounds, alone or in combination with other therapeutic agents, for the inhibition of platelet aggregation, as thrombolytics and/or for the treatment of thromboembolic disorders.

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TITLE

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Novel Isoxazoline and Isoxazole Fibrinogen Receptor
Antagonists

Cross Reference to Earlier Filed Application

10 This application is a continuation-in-part of U.S. Patent Application Serial Number 08/232,961, filed April 22, 1994 which is a continuation-in-part of U.S. Patent Application Serial Number 08/157,598, filed November 24, 1993. The disclosures of these earlier filed 15 applications are hereby incorporated herein by reference.

FIELD OF THE INVENTION

20 This invention relates to novel isoxazolines and isoxazoles which are useful as antagonists of the platelet glycoprotein IIb/IIIa fibrinogen receptor complex, to pharmaceutical compositions containing such compounds, processes for preparing such compounds, and 25 to methods of using these compounds, alone or in combination with other therapeutic agents, for the inhibition of platelet aggregation, as thrombolytics, and/or for the treatment of thromboembolic disorders.

30

BACKGROUND OF THE INVENTION

Hemostasis is the normal physiological process in which bleeding from an injured blood vessel is arrested. It is a dynamic and complex process in which platelets 35 play a key role. Within seconds of vessel injury, resting platelets become activated and are bound to the

exposed matrix of the injured area by a phenomenon called platelet adhesion. Activated platelets also bind to each other in a process called platelet aggregation to form a platelet plug. The platelet plug can stop 5 bleeding quickly, but it must be reinforced by fibrin for long-term effectiveness, until the vessel injury can be permanently repaired.

Thrombosis may be regarded as the pathological condition wherein improper activity of the hemostatic 10 mechanism results in intravascular thrombus formation. Activation of platelets and the resulting platelet aggregation and platelet factor secretion has been associated with a variety of pathophysiological conditions including cardiovascular and cerebrovascular 15 thromboembolic disorders, for example, the thromboembolic disorders associated with unstable angina, myocardial infarction, transient ischemic attack, stroke, atherosclerosis and diabetes. The contribution of platelets to these disease processes 20 stems from their ability to form aggregates, or platelet thrombi, especially in the arterial wall following injury.

Platelets are activated by a wide variety of agonists resulting in platelet shape change, secretion 25 of granular contents and aggregation. Aggregation of platelets serves to further focus clot formation by concentrating activated clotting factors at the site of injury. Several endogenous agonists including adenosine diphosphate (ADP), serotonin, arachidonic acid, 30 thrombin, and collagen, have been identified. Because of the involvement of several endogenous agonists in activating platelet function and aggregation, an inhibitor which acts against all agonists would represent a more efficacious antiplatelet agent than 35 currently available antiplatelet drugs, which are agonist-specific.

Current antiplatelet drugs are effective against only one type of agonist; these include aspirin, which acts against arachidonic acid; ticlopidine, which acts against ADP; thromboxane A₂ synthetase inhibitors or receptor antagonists, which act against thromboxane A₂; and hirudin, which acts against thrombin.

Recently, a common pathway for all known agonists has been identified, namely platelet glycoprotein IIb/IIIa complex (GPIIb/IIIa), which is the membrane protein mediating platelet aggregation. A recent review of GPIIb/IIIa is provided by Phillips et al. *Cell* (1991) 65: 359-362. The development of a GPIIb/IIIa antagonist represents a promising new approach for antiplatelet therapy.

GPIIb/IIIa does not bind soluble proteins on unstimulated platelets, but GPIIb/IIIa in activated platelets is known to bind four soluble adhesive proteins, namely fibrinogen, von Willebrand factor, fibronectin, and vitronectin. The binding of fibrinogen and von Willebrand factor to GPIIb/IIIa causes platelets to aggregate. The binding of fibrinogen is mediated in part by the Arg-Gly-Asp (RGD) recognition sequence which is common to the adhesive proteins that bind GPIIb/IIIa.

In addition to GPIIb/IIIa, increasing numbers of other cell surface receptors have been identified which bind to extracellular matrix ligands or other cell adhesion ligands thereby mediating cell-cell and cell-matrix adhesion processes. These receptors belong to a gene superfamily called integrins and are composed of heterodimeric transmembrane glycoproteins containing α - and β -subunits. Integrin subfamilies contain a common β -subunit combined with different α -subunits to form adhesion receptors with unique specificity. The genes for eight distinct β -subunits have been cloned and sequenced to date.

-4-

Two members of the β_1 subfamily, α_4/β_1 and α_5/β_1 have been implicated in various inflammatory processes.

Antibodies to α_4 prevent adhesion of lymphocytes to synovial endothelial cells *in vitro*, a process which may 5 be of importance in rheumatoid arthritis (VanDinther-Janssen et al., *J. Immunol.*, 1991, 147:4207).

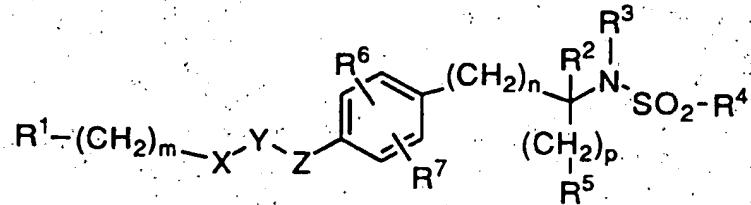
Additional studies with monoclonal anti- α_4 antibodies provide evidence that α_4/β_1 may additionally have a role 10 in allergy, asthma, and autoimmune disorders (Walsh et al., *J. Immunol.*, 1991, 146:3419; Bochner et al., *J. Exp. Med.*, 1991, 173:1553; Yednock et al., *Nature*, 1992, 356:63). Anti- α_4 antibodies also block the migration of leukocytes to the site of inflammation (Issedutz et al., *J. Immunol.*, 1991, 147:4178).

15 The α_v/β_3 heterodimer, commonly referred to as the vitronectin receptor, is another member of the β_3 integrin subfamily and has been described in platelets, endothelial cells, melanoma, smooth muscle cells and on the surface of osteoclasts (Horton and Davies, *J. Bone 20 Min. Res.* 1989, 4:803-808; Davies et al., *J. Cell. Biol.*, 1989, 109:1817-1826; Horton, *Int. J. Exp. Pathol.*, 1990, 71:741-759). Like GPIIb/IIIa, the vitronectin receptor binds a variety of RGD-containing adhesive proteins such as vitronectin, fibronectin, VWF, fibrinogen, 25 osteopontin, bone sialo protein II and thrombospondin in a manner mediated by the RGD sequence. Possible roles for α_v/β_3 in angiogenesis, tumor progression, and neovascularization have been proposed (Brooks et al., *Science*, 1994, 264:569-571). A key event in bone 30 resorption is the adhesion of osteoclasts to the matrix of bone. Studies with monoclonal antibodies have implicated the α_v/β_3 receptor in this process and suggest that a selective α_v/β_3 antagonist would have utility in blocking bone resorption (Horton et al., *J. Bone Miner. Res.*, 1993, 8:239-247; Helfrich et al., *J. Bone Miner. Res.*, 1992, 7:335-343).

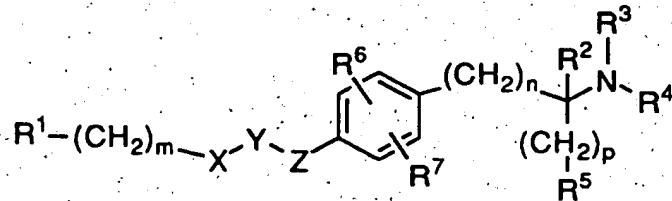
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Several RGD-peptidomimetic compounds have been reported which block fibrinogen binding and prevent the formation of platelet thrombi.

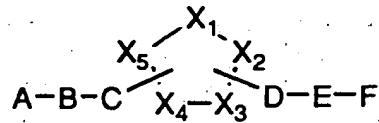
5 European Patent Application Publication Number 478363 relates to compounds having the general formula:



10 European Patent Application Publication Number 478328 relates to compounds having the general formula:



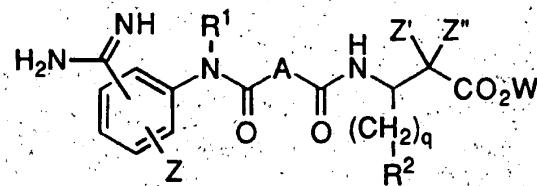
15 European Patent Application Publication Number 525629 (corresponds to Canadian Patent Application Publication Number 2,074,685) discloses compounds having the general formula:



20

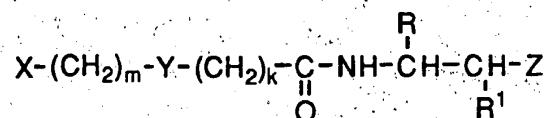
PCT Patent Application 9307867 relates to compounds having the general formula:

-6-



European Patent Application Publication Number
4512831 relates to compounds having the general formula:

5



None of the above references teaches or suggests
the compounds of the present invention which are
10 described in detail below.

SUMMARY OF THE INVENTION

The present invention provides novel nonpeptide compounds which bind to integrin receptors thereby 5 altering cell-matrix and cell-cell adhesion processes. The compounds of the present invention are useful for the treatment of inflammation, bone degradation, tumors, metastases, thrombosis, cell aggregation-related conditions in a mammal.

10 One aspect of this invention provides novel compounds of Formula I (described below) which are useful as antagonists of the platelet glycoprotein IIb/IIIa complex. The compounds of the present invention inhibit the binding of fibrinogen to platelet 15 glycoprotein IIb/IIIa complex and inhibit the aggregation of platelets. The present invention also includes pharmaceutical compositions containing such compounds of Formula I, and methods of using such compounds for the inhibition of platelet aggregation, as 20 thrombolytics, and/or for the treatment of thromboembolic disorders.

The present invention also includes methods of treating cardiovascular disease, thrombosis or harmful platelet aggregation, reocclusion following 25 thrombolysis, reperfusion injury, or restenosis by administering a compound of Formula I alone or in combination with one or more additional therapeutic agents selected from: anti-coagulants such as warfarin or heparin; anti-platelet agents such as aspirin, 30 piroxicam or ticlopidine; thrombin inhibitors such as boroarginine derivatives, hirudin or argatroban; or thrombolytic agents such as tissue plasminogen activator, anistreplase, urokinase or streptokinase; or combinations thereof.

Aspirin.

-8-

The present invention also provides novel compounds, pharmaceutical compositions and methods which may be used in the treatment or prevention of diseases which involve cell adhesion processes, including, but not limited to, rheumatoid arthritis, asthma, allergies, adult respiratory distress syndrome, graft versus host disease, organ transplantation, septic shock, psoriasis, eczema, contact dermatitis, osteoporosis, osteoarthritis, atherosclerosis, metastasis, wound healing, diabetic retinopathy, inflammatory bowel disease and other autoimmune diseases.

Also included in the present invention are pharmaceutical kits comprising one or more containers containing pharmaceutical dosage units comprising a compound of Formula I, for the treatment of cell adhesion related disorders, including but not limited to thromboembolic disorders.

DETAILED DESCRIPTION OF THE INVENTION

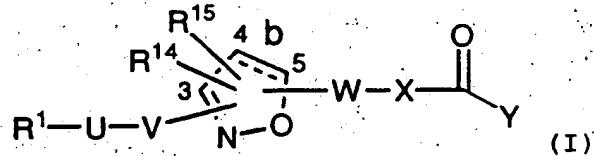
The present invention provides novel nonpeptide compounds of Formula I (described below) which bind to integrin receptors thereby altering cell-matrix and cell-cell adhesion processes. The compounds of the present invention are useful for the treatment of inflammation, bone degradation, tumors, metastases, thrombosis, cell aggregation-related conditions in a mammal.

One aspect of this invention provides compounds of Formula I (described below) which are useful as antagonists of the platelet glycoprotein IIb/IIIa complex. The compounds of the present invention inhibit the binding of fibrinogen to the platelet glycoprotein IIb/IIIa complex and inhibit the aggregation of platelets. The present invention also includes pharmaceutical compositions containing such compounds of

-9-

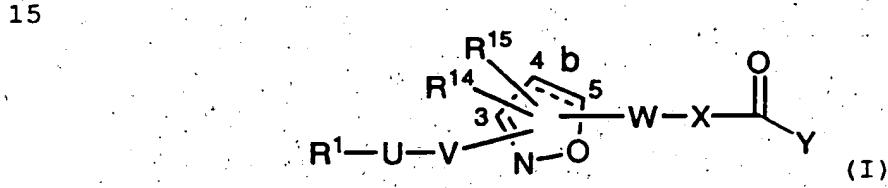
Formula I, and methods of using such compounds for the inhibition of platelet aggregation, as thrombolytics, and/or for the treatment of thromboembolic disorders.

5 This invention relates to novel compounds of the Formula I:



10 or a pharmaceutically acceptable salt or prodrug form thereof.

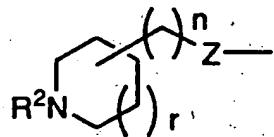
[1] A first embodiment of this invention provides compounds of Formula I:



or pharmaceutically acceptable salt or prodrug forms thereof wherein:

20 b is a single or double bond;

R¹ is selected from R²(R³)N(CH₂)ₖZ-, R²(R³)N(R²N=)CN(R²)(CH₂)ₖZ-, piperazinyl-(CH₂)ₖZ- or



25

Z is selected from O, S, S(=O), or S(=O)₂;

-10-

R² and R³ are independently selected from: H, C₁-C₁₀ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, C₆-C₁₀ aryl, C₇-C₁₁ arylalkyl, C₂-C₇ alkylcarbonyl, C₆-C₁₀ arylcarbonyl, C₂-C₁₀ alkoxycarbonyl, C₄-C₁₁ cycloalkoxycarbonyl, C₇-C₁₁ bicycloalkoxycarbonyl, C₆-C₁₀ aryloxycarbonyl, aryl(C₁-C₁₀ alkoxy)carbonyl, C₁-C₆ alkylcarbonyloxy(C₁-C₄ alkoxy)carbonyl, C₆-C₁₀ arylcarbonyloxy(C₁-C₄ alkoxy)carbonyl, C₄-C₁₁ cycloalkylcarbonyloxy(C₁-C₄ alkoxy)carbonyl;

U is selected from:

a single bond (i.e., U is not present),

-(C₁-C₇ alkyl)-,

15 -(C₂-C₇ alkenyl)-,

-(C₂-C₇ alkynyl)-,

-(aryl)- substituted with 0-3 R^{6a}, or

-(pyridyl)- substituted with 0-3 R^{6a};

20 V is selected from:

a single bond (i.e., V is not present);

-(C₁-C₇ alkyl)-, substituted with 0-3 groups

independently selected from R⁶ or R⁷;

-(C₂-C₇ alkenyl)-, substituted with 0-3 groups

independently selected from R⁶ or R⁷;

-(C₂-C₇ alkynyl)-, substituted with 0-2 groups

independently selected from R⁶ or R⁷;

-(aryl)-, substituted with 0-2 groups

independently selected from R⁶ or R⁷;

30 -(pyridyl)-, substituted with 0-2 groups

independently selected from R⁶ or R⁷; or

-(pyridazinyl)-, substituted with 0-2 groups

independently selected from R⁶ or R⁷;

35 W is selected from:

-11-

a single bond (i.e., W is not present),

-(C₁-C₇ alkyl)-,

-(C₂-C₇ alkenyl)-,

-(C₂-C₇ alkynyl)-, or

5 -(C(R⁵)₂)_nC(=O)N(R^{5a})-;

X is selected from:

a single bond (i.e., X is not present);

-(C₁-C₇ alkyl)-, substituted with 0-3 groups

10 independently selected from R⁴, R⁸ or R¹⁴;

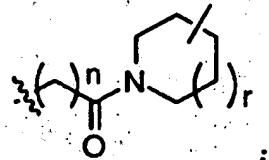
-(C₂-C₇ alkenyl)-, substituted with 0-3 groups

independently selected from R⁴, R⁸ or R¹⁴;

-(C₂-C₇ alkynyl)-, substituted with 0-2 groups

independently selected from R⁴, R⁸ or R¹⁴; or

15



Y is selected from hydroxy, C₁ to C₁₀ alkyloxy, C₃ to

C₁₁ cycloalkyloxy, C₆ to C₁₀ aryloxy, C₇ to C₁₁

20 aralkyloxy, C₃ to C₁₀ alkylcarbonyloxyalkyloxy, C₃ to

C₁₀ alkoxy carbonyloxyalkyloxy, C₂ to C₁₀

alkoxycarbonylalkyloxy, C₅ to C₁₀

cycloalkylcarbonyloxyalkyloxy, C₅ to C₁₀

cycloalkoxycarbonyloxyalkyloxy, C₅ to C₁₀

25 cycloalkoxycarbonylalkyloxy, C₇ to C₁₁

aryloxycarbonylalkyloxy, C₈ to C₁₂

aryloxycarbonyloxyalkyloxy, C₈ to C₁₂

arylcarbonyloxyalkyloxy, C₅ to C₁₀

alkoxyalkylcarbonyloxyalkyloxy, C₅ to C₁₀ (5-alkyl-

30 1,3-dioxa-cyclopenten-2-one-yl)methyloxy, C₁₀ to C₁₄

(5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy;

or (R²)(R³)N-(C₁-C₁₀ alkoxy)-;

-12-

40 R⁴ and R^{4b} are independently selected from H, C₁-C₁₀ alkyl, hydroxy, C₁-C₁₀ alkoxy, nitro, C₁-C₁₀ alkylcarbonyl, or -N(R¹²)R¹³;

45 R⁵ is selected from H, C₁-C₈ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylmethyl, C₆-C₁₀ aryl, C₇-C₁₁ arylalkyl, or C₁-C₁₀ alkyl substituted with 0-2 R^{4b};

50 R^{5a} is selected from hydrogen, hydroxy, C₁ to C₈ alkyl, C₂ to C₆ alkenyl, C₃ to C₁₁ cycloalkyl, C₄ to C₁₁ cycloalkylmethyl, C₁-C₆ alkoxy, benzyloxy, C₆ to C₁₀ aryl, heteroaryl, heteroarylalkyl, C₇ to C₁₁ arylalkyl, adamantylmethyl or C₁-C₁₀ alkyl

55 substituted with 0-2 R^{4b};

60 alternately, R⁵ and R^{5a} can be taken together to be 3-azabicyclononyl, 1-piperidinyl, 1-morpholinyl or 1-piperazinyl, each being optionally substituted with C₁-C₆ alkyl, C₆-C₁₀ aryl, heteroaryl, C₇-C₁₁ arylalkyl, C₁-C₆ alkylcarbonyl, C₃-C₇ cycloalkylcarbonyl, C₁-C₆ alkoxy carbonyl, C₇-C₁₁ arylalkoxycarbonyl, C₁-C₆ alkylsulfonyl or C₆-C₁₀ arylsulfonyl;

65 R^{5b} is selected from C₁-C₈ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylmethyl, C₆-C₁₀ aryl, C₇-C₁₁ arylalkyl, or C₁-C₁₀ alkyl substituted with 0-2 R^{4b};

70 R⁶ is selected from H, C₁-C₁₀ alkyl, hydroxy, C₁-C₁₀ alkoxy, nitro, C₁-C₁₀ alkylcarbonyl, -N(R¹²)R¹³, cyano, halo, CF₃, CHO, CO₂R⁵, C(=O)R^{5a}, CONR⁵R^{5a}, OC(=O)R^{5a}, OC(=O)OR^{5b}, OR^{5a}, OC(=O)NR⁵R^{5a}, OCH₂CO₂R⁵, CO₂CH₂CO₂R⁵, NO₂, NR^{5a}C(=O)R^{5a}, NR^{5a}C(=O)OR^{5b},

-13-

NR^{5a}C(=O)NR^{5a}R^{5a}, NR^{5a}SO₂NR^{5a}R^{5a}, NR^{5a}SO₂R⁵, S(O)_pR^{5a},
SO₂NR^{5a}R^{5a}, C₂ to C₆ alkenyl, C₃ to C₁₁ cycloalkyl,
C₄ to C₁₁ cycloalkylmethyl;

5 C₆ to C₁₀ aryl optionally substituted with 1-3 groups selected from halogen, C₁-C₆ alkoxy, C₁-C₆ alkyl, CF₃, S(O)_mMe, or -NMe₂;

10 C₇ to C₁₁ arylalkyl, said aryl being optionally substituted with 1-3 groups selected from halogen, C₁-C₆ alkoxy, C₁-C₆ alkyl, CF₃, S(O)_mMe, or -NMe₂;
methylenedioxy when R⁶ is a substituent on aryl; or

15 a 5-10 membered heterocyclic ring containing 1-3 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-2 R⁷;

20 R^{6a} is selected from C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, CF₃, NO₂, or NR¹²R¹³;

25 R⁷ is selected from H, C₁-C₁₀ alkyl, hydroxy, C₁-C₁₀ alkoxy, nitro, C₁-C₁₀ alkylcarbonyl, -N(R¹²)R¹³, cyano, halo, CF₃, CHO, CO₂R⁵, C(=O)R^{5a}, CONR^{5a}R^{5a}, OC(=O)R^{5a}, OC(=O)OR^{5b}, OR^{5a}, OC(=O)NR^{5a}R^{5a}, OCH₂CO₂R⁵, CO₂CH₂CO₂R⁵, NO₂, NR^{5a}C(=O)R^{5a}, NR^{5a}C(=O)OR^{5b}, NR^{5a}C(=O)NR^{5a}R^{5a}, NR^{5a}SO₂NR^{5a}R^{5a}, NR^{5a}SO₂R⁵, S(O)_pR^{5a}, SO₂NR^{5a}R^{5a}, C₂ to C₆ alkenyl, C₃ to C₁₁ cycloalkyl, C₄ to C₁₁ cycloalkylmethyl, C₆ to C₁₀ aryl, or C₇ to C₁₁ arylalkyl;

30 R⁸ is selected from:
35 H;

-14-

R⁶;C₁-C₁₀ alkyl, substituted with 0-3 R⁶;C₂-C₁₀ alkenyl, substituted with 0-3 R⁶;C₂-C₁₀ alkynyl, substituted with 0-3 R⁶;5 C₃-C₈ cycloalkyl, substituted with 0-3 R⁶;C₅-C₆ cycloalkenyl, substituted with 0-2 R⁶;aryl, substituted with 0-2 R⁶;

5-10 membered heterocyclic ring containing 1-3 N,

O, or S heteroatoms, wherein said heterocyclic

10 ring may be saturated, partially saturated, or

fully unsaturated, said heterocyclic ring

being substituted with 0-2 R⁶;R¹² and R¹³ are independently H, C₁-C₁₀ alkyl, C₁-C₁₀15 alkoxycarbonyl, C₁-C₁₀ alkylcarbonyl, C₁-C₁₀alkylsulfonyl, aryl(C₁-C₁₀ alkyl)sulfonyl,arylsulfonyl, aryl, C₂-C₆ alkenyl, C₃-C₁₁cycloalkyl, C₄-C₁₁ cycloalkylalkyl, C₇-C₁₁arylalkyl, C₂-C₇ alkylcarbonyl, C₇-C₁₁ arylcarbonyl,20 C₂-C₁₀ alkoxycarbonyl, C₄-C₁₁ cycloalkoxycarbonyl,C₇-C₁₁ bicycloalkoxycarbonyl, C₇-C₁₁

aryloxycarbonyl, heteroarylcarbonyl,

heteroarylalkylcarbonyl or

aryl(C₁-C₁₀ alkoxy)carbonyl;

25

R¹⁴ is selected from H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl,C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, aryl, heteroaryl orC₁-C₁₀ alkoxycarbonyl, CO₂R⁵ or -C(=O)N(R⁵)R^{5a};30 R¹⁵ is selected from:

H;

R⁶;C₁-C₁₀ alkyl, substituted with 0-8 R⁶;C₂-C₁₀ alkenyl, substituted with 0-6 R⁶;35 C₁-C₁₀ alkoxy, substituted with 0-6 R⁶;

-15-

aryl, substituted with 0-5 R⁶;

5 5-6 membered heterocyclic ring containing 1-2 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-5 R⁶;

10 C₁-C₁₀ alkoxy carbonyl substituted with 0-8 R⁶;

CO₂R⁵; or

-C(=O)N(R⁵)R^{5a};

15 n is 0-4;

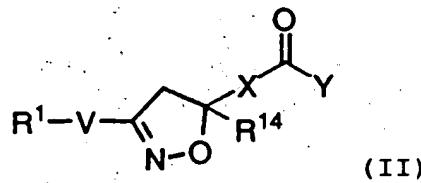
q is 2-7;

r is 0-3;

20 15 provided that when b is a double bond, only one of R¹⁴ or R¹⁵ is present;

provided that n, q, and r are chosen such that the number of in-chain atoms between R¹ and Y is in the 20 range of 8-18.

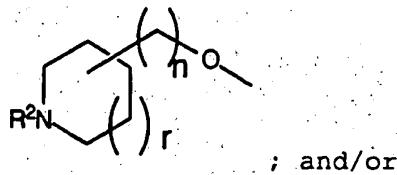
25 [2] Preferred compounds of this first embodiment are those of Formula II (where W is a single bond (i.e., absent) and U is a single bond (i.e., absent)):



wherein:

30 R¹ is selected from R²HN(CH₂)_qO-, R²HN(R²N=)CNH(CH₂)_qO-, piperazinyl-(CH₂)_qO-, or

-16-



; and/or

20 R^2 is selected from H, aryl(C_1-C_{10} alkoxy)carbonyl, C_1-C_{10} alkoxy carbonyl; and/or

5

5 R^8 is selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_3-C_8 cycloalkyl, C_5-C_6 cycloalkenyl, aryl, 5-6 membered heterocyclic ring containing 1-2 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated; and/or

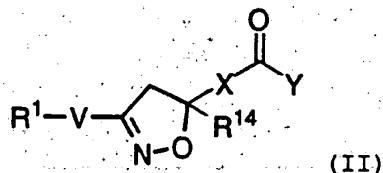
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10 R^6 and R^7 are selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, 15 $-N(R^{12})R^{13}$, cyano, or halo.

15

[3] Further preferred compounds of this first embodiment are those of Formula II (where W is a bond/absent and U is a bond/absent):

20



wherein:

25 X is selected from:

- a single bond (i.e., X is not present);
- $-(C_1-C_7$ alkyl)-, substituted with 0-2 groups independently selected from R^4 , R^8 or R^{14} ;

-17-

-(C₂-C₇ alkenyl)-, substituted with 0-2 groups
 independently selected from R⁴, R⁸ or R¹⁴;
 -(C₂-C₇ alkynyl)-, substituted with 0-2 groups

independently selected from R⁴, R⁸ or R¹⁴;
 and/or

5

10

15

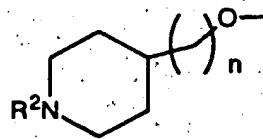
R⁸ is selected from H, C₁-C₆ alkyl, C₂-C₆ alkenyl,
 C₃-C₈ cycloalkyl, C₅-C₆ cycloalkenyl, aryl, 5-6
 membered heterocyclic ring containing 1-2 N, O, or
 S heteroatoms, wherein said heterocyclic ring may
 be saturated, partially saturated, or fully
 unsaturated.

20

25

[4] Further preferred compounds of this first
 embodiment are compounds of Formula I wherein:

R¹ is



V is phenylene or pyridylene;

n is 1 or 2;

X is -(C₁-C₂)alkyl- substituted with 0-2 R⁴

25

30

Y is selected from:

hydroxy;

C₁ to C₁₀ alkoxy;

methylcarbonyloxymethoxy-;

ethylcarbonyloxymethoxy-;

t-butylcarbonyloxymethoxy-;

cyclohexylcarbonyloxymethoxy-;

1-(methylcarbonyloxy)ethoxy-;

-18-

1-(ethylcarbonyloxy)ethoxy-;
1-(t-butyloxycarbonyloxy)ethoxy-;
1-(cyclohexylcarbonyloxy)ethoxy-;
5 i-propyloxycarbonyloxymethoxy-;
t-butyloxycarbonyloxymethoxy-;
1-(i-propyloxycarbonyloxy)ethoxy-;
1-(cyclohexyloxycarbonyloxy)ethoxy-;
1-(t-butyloxycarbonyloxy)ethoxy-;
dimethylaminoethoxy-;
10 diethylaminoethoxy-;
(5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;
(5-(t-butyl)-1,3-dioxacyclopenten-2-on-4-
y1)methoxy-;
(1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methoxy-;
15 1-(2-(2-methoxypropyl)carbonyloxy)ethoxy-;

R⁴ is -NR¹²R¹³;

20 R¹² is H, C₁-C₄ alkoxy carbonyl, C₁-C₄ alkyl carbonyl, C₁-
C₄ alkylsulfonyl, arylalkylsulfonyl, arylsulfonyl,
benzyl, benzoyl, phenoxy carbonyl,
benzyloxycarbonyl, arylalkylsulfonyl,
pyridyl carbonyl, or pyridylmethyl carbonyl;

25 R¹³ is H.

[5] Specifically preferred compounds of this first embodiment are compounds, or pharmaceutically acceptable salt or prodrug forms thereof, selected from:

30

5 (R,S)-3-[(4-(2-piperidin-4-yl)ethoxyphenyl]isoxazolin-
5-yl]acetic acid;

5 (R,S)-N-(butanesulfonyl)-L-(3-[4-(2-piperidin-4-
y1)ethoxyphenyl]isoxazolin-5-yl)glycine;

35

5 (R,S)-N-(α -toluenesulfonyl)-L-(3-[4-(2-piperidin-4-
y1)ethoxyphenyl]isoxazolin-5-yl)glycine;

-19-

5 (R, S)-N-[(benzyloxy)carbonyl]-L-{3-[4-(2-piperidin-4-yl)ethoxyphenyl]isoxazolin-5-yl}glycine;

5 (R, S)-N-(pentanoyl)-L-{3-[4-(2-piperidin-4-yl)ethoxyphenyl]isoxazolin-5-yl}glycine;

5 5 (R, S)-3-[(4-(piperidin-4-yl)methoxyphenyl)isoxazolin-5-yl]propanoic acid;

2 (R, S)-5 (R, S)-N-(butanesulfonyl)amino-{3-[4-(piperidin-4-yl)methoxyphenyl]isoxazolin-5-yl}propanoic acid;

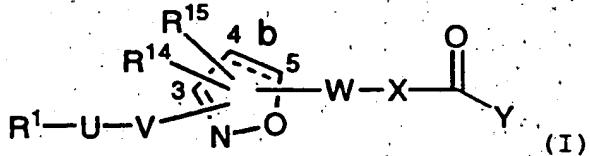
2 (R, S)-5 (R, S)-N-(α -toluenesulfonyl)amino-{3-[4-(piperidin-4-yl)methoxyphenyl]isoxazolin-5-yl}propanoic acid;

10 2 (R, S)-5 (R, S)-N-[(benzyloxy)carbonyl]amino-{3-[4-(piperidin-4-yl)methoxyphenyl]isoxazolin-5-yl}propanoic acid;

15 2 (R, S)-5 (R, S)-N-(pentanoyl)amino-{3-[4-(piperidin-4-yl)methoxyphenyl]isoxazolin-5-yl}propanoic acid.

[6] A second embodiment of this invention provides a compound of Formula I:

20



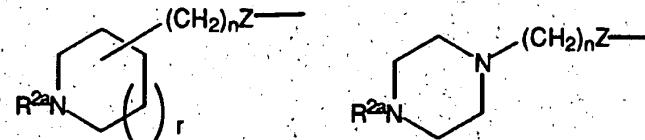
or a pharmaceutically acceptable salt or prodrug form thereof wherein:

25

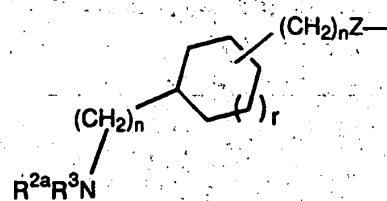
b is a single or double bond;

R¹ is selected from R^{2a}(R³)N-, R²(R³)N(R²N=)C-,
 R^{2a}(R³)N(CH₂)_qZ-, R²(R³)N(R²N=)C(CH₂)_qZ-,
 30 R²(R³)N(R²N=)CN(R²)-,

-20-



or



5 Z is selected from a bond (i.e. is absent), O, S, S(=O),
S(=O)₂;

R² and R³ are independently selected from: H, C₁-C₁₀
alkyl, C₃-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁
10 cycloalkylalkyl, C₆-C₁₀ aryl, C₇-C₁₁ arylalkyl, C₂-C₇
alkylcarbonyl, C₇-C₁₁ arylcarbonyl, C₂-C₁₀
alkoxycarbonyl, C₄-C₁₁ cycloalkoxycarbonyl, C₇-C₁₁
15 bicycloalkoxycarbonyl, C₇-C₁₁ aryloxycarbonyl,
aryl(C₁-C₁₀ alkoxy)carbonyl, C₁-C₆
alkylcarbonyloxy(C₁-C₄ alkoxy)carbonyl, C₆-C₁₀
arylcarbonyloxy(C₁-C₄ alkoxy)carbonyl, C₄-C₁₁
20 cycloalkylcarbonyloxy(C₁-C₄ alkoxy)carbonyl;;

R^{2a} is R² or R²(R³)N(R²N=)C-;

20

U is selected from:

a single bond (i.e., U is not present),
-(C₁-C₇ alkyl)-,
-(C₂-C₇ alkenyl)-,
25 -(C₂-C₇ alkynyl)-,
-(aryl)- substituted with 0-3 R^{6a}, or
-(pyridyl)- substituted with 0-3 R^{6a};

V is selected from:

-21-

a single bond (i.e., V is not present);
-(C₁-C₇ alkyl)-, substituted with 0-3 groups
independently selected from R⁶ or R⁷;

5. -(C₂-C₇ alkenyl)-, substituted with 0-3 groups
independently selected from R⁶ or R⁷;
-(C₂-C₇ alkynyl)-, substituted with 0-3 groups
independently selected from R⁶ or R⁷;
-(phenyl)-Q-, said phenyl substituted with 0-2
groups independently selected from R⁶ or R⁷;
10 -(pyridyl)-Q-, said pyridyl substituted with 0-2
groups independently selected from R⁶ or R⁷; or
-(pyridazinyl)-Q-, said pyridazinyl substituted
with 0-2 groups independently selected from R⁶
or R⁷.

15 Q is selected from:
a single bond (i.e., Q is not present),
-O-, -S(O)_m-, -N(R¹²)-, -(CH₂)_m-, -C(=O)-,
-N(R^{5a})C(=O)-, -C(=O)N(R^{5a})-, -CH₂O-, -OCH₂-,
20 -CH₂N(R¹²)-, -N(R¹²)CH₂-, -CH₂C(=O)-, -C(=O)CH₂-,
-CH₂S(O)_m-, or -S(O)_mCH₂-,

provided that when b is a single bond, and R¹-U-V-
is a substituent on C5 of the central 5-membered
25 ring of Formula I, then Q is not -O-, -S(O)_m-,
-N(R¹²)-, -C(=O)N(R^{5a})-, -CH₂O-, CH₂N(R¹²)- or
-CH₂S(O)_m-;

30 W is selected from:
-(C(R⁴)₂)_nC(=O)N(R^{5a})-, or
-C(=O)-N(R^{5a})-(C(R⁴)₂)_n-;

X is selected from:
a single bond (i.e. X is absent)

-22-

$-(C(R^4)_2)_n-C(R^4)(R^8)-C(R^4)(R^{4a})-$, with the proviso that when n is 0 or 1, then at least one of R^{4a} or R^8 is other than H or methyl;

5. Y is selected from hydroxy, C_1 to C_{10} alkyloxy, C_3 to C_{11} cycloalkyloxy, C_6 to C_{10} aryloxy, C_7 to C_{11} aralkyloxy, C_3 to C_{10} alkylcarbonyloxyalkyloxy, C_3 to C_{10} alkoxy carbonyloxyalkyloxy, C_2 to C_{10} alkoxy carbonylalkyloxy, C_5 to C_{10}

10 cycloalkylcarbonyloxyalkyloxy, C_5 to C_{10} cycloalkoxycarbonyloxyalkyloxy, C_5 to C_{10} cycloalkoxycarbonylalkyloxy, C_7 to C_{11}

aryloxy carbonylalkyloxy, C_8 to C_{12}

aryloxy carbonyloxyalkyloxy, C_8 to C_{12}

15 arylcarbonyloxyalkyloxy, C_5 to C_{10} alkoxyalkylcarbonyloxyalkyloxy, C_5 to C_{10} (5-alkyl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy, C_{10} to C_{14}

(5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy,

$(R^2)(R^3)N-(C_1-C_{10}$ alkoxy)-;

20

R^4 is selected from H, C_1-C_{10} alkyl, C_1-C_{10} alkylcarbonyl, aryl, arylalkyl, cycloalkyl, or cycloalkylalkyl;

25

alternately, two R^4 groups on adjacent carbons may join to form a bond (i.e. a carbon-carbon double or triple bond);

30

R^{4a} is selected from H, hydroxy, C_1-C_{10} alkoxy, nitro, $N(R^5)R^{5a}$, $-N(R^{12})R^{13}$, $-N(R^{16})R^{17}$, C_1-C_{10} alkyl substituted with 0-3 R^6 , aryl substituted with 0-3 R^6 , heteroaryl substituted with 0-3 R^6 or C_1-C_{10} alkylcarbonyl;

35

-23-

5 R^{4b} is selected from H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, C₇-C₁₄ bicycloalkyl, hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₆ alkylsulfinyl, C₁-C₆ alkylsulfonyl, nitro, C₁-C₆ alkylcarbonyl, C₆-C₁₀ aryl, -N(R¹²)R¹³; halo, CF₃, CN, C₁-C₆ alkoxy carbonyl, carboxy, piperidinyl, morpholinyl or pyridinyl;

10 R^5 is selected from H, C₁-C₈ alkyl, C₃-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylmethyl, C₆-C₁₀ aryl, C₇-C₁₁ arylalkyl, or C₁-C₁₀ alkyl substituted with 0-2 R^{4b} ;

15 R^{5a} is selected from hydrogen, hydroxy, C₁ to C₈ alkyl, C₃-C₆ alkenyl, C₃ to C₁₁ cycloalkyl, C₄ to C₁₁ cycloalkylmethyl, C₁-C₆ alkoxy, benzyloxy, C₆ to C₁₀ aryl, heteroaryl, heteroarylalkyl, C₇ to C₁₁ arylalkyl, adamantylmethyl, or C₁-C₁₀ alkyl substituted with 0-2 R^{4b} ;

20 alternately, R^5 and R^{5a} when both are substituents on the same nitrogen atom (as in -NR⁵R^{5a}) can be taken together with the nitrogen atom to which they are attached to form 3-azabicyclononyl, 1,2,3,4-tetrahydro-1-quinolinyl, 1,2,3,4-tetrahydro-2-isouquinolinyl, 1-piperidinyl, 1-morpholinyl, 1-pyrrolidinyl, thiamorpholinyl, thiazolidinyl or 1-piperazinyl, each being optionally substituted with C₁-C₆ alkyl, C₆-C₁₀ aryl, heteroaryl, C₇-C₁₁ arylalkyl, C₁-C₆ alkylcarbonyl, C₃-C₇ cycloalkylcarbonyl, C₁-C₆ alkoxy carbonyl, C₇-C₁₁ arylalkoxy carbonyl, C₁-C₆ alkylsulfonyl or C₆-C₁₀ arylsulfonyl;

-24-

R^{5b} is selected from C_1-C_8 alkyl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylmethyl, C_6-C_{10} aryl, C_7-C_{11} arylalkyl, or C_1-C_{10} alkyl substituted with 0-2 R^{4b} ;

5

R^6 is selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, $-N(R^{12})R^{13}$, cyano, halo, CF_3 , CHO , CO_2R^5 , $C(=O)R^{5a}$, $CONR^{5a}R^{5a}$, $OC(=O)R^{5a}$, $OC(=O)OR^{5b}$, OR^{5a} , $OC(=O)NR^{5a}R^{5a}$, $OCH_2CO_2R^5$, $CO_2CH_2CO_2R^5$, NO_2 , $NR^{5a}C(=O)R^{5a}$, $NR^{5a}C(=O)OR^{5b}$, $NR^{5a}C(=O)NR^{5a}R^{5a}$, $NR^{5a}SO_2NR^{5a}R^{5a}$, $NR^{5a}SO_2R^5$, $S(O)_mR^{5a}$, $SO_2NR^{5a}R^{5a}$, $SiMe_3$, C_2 to C_6 alkenyl, C_3 to C_{11} cycloalkyl, C_4 to C_{11} cycloalkylmethyl;

15

C_6 to C_{10} aryl optionally substituted with 1-3 groups selected from halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3 , $S(O)_mMe$, or $-NMe_2$;

20

C_7 to C_{11} arylalkyl, said aryl being optionally substituted with 1-3 groups selected from halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3 , $S(O)_mMe$, or $-NMe_2$;

methylenedioxy when R^6 is a substituent on aryl; or

25

a 5-10 membered heterocyclic ring containing 1-3 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-2 R^7 ;

30

R^{6a} is selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, CF_3 , NO_2 , or $NR^{12}R^{13}$;

R^7 is selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10}

35

alkoxy, nitro, C_1-C_{10} alkylcarbonyl, $-N(R^{12})R^{13}$,

-25-

cyano, halo, CF_3 , CHO , CO_2R^5 , $\text{C}(=\text{O})\text{R}^5\text{a}$, $\text{CONR}^5\text{R}^5\text{a}$,
 $\text{OC}(=\text{O})\text{R}^5\text{a}$, $\text{OC}(=\text{O})\text{OR}^5\text{b}$, OR^5a , $\text{OC}(=\text{O})\text{NR}^5\text{R}^5\text{a}$, $\text{OCH}_2\text{CO}_2\text{R}^5$,
 $\text{CO}_2\text{CH}_2\text{CO}_2\text{R}^5$, NO_2 , $\text{NR}^5\text{aC}(=\text{O})\text{R}^5\text{a}$, $\text{NR}^5\text{aC}(=\text{O})\text{OR}^5\text{b}$,
5 $\text{NR}^5\text{aC}(=\text{O})\text{NR}^5\text{R}^5\text{a}$, $\text{NR}^5\text{aSO}_2\text{NR}^5\text{R}^5\text{a}$, $\text{NR}^5\text{aSO}_2\text{R}^5$, $\text{S(O)}_m\text{R}^5\text{a}$,
 $\text{SO}_2\text{NR}^5\text{R}^5\text{a}$, C_2 to C_6 alkenyl, C_3 to C_{11} cycloalkyl,
 C_4 to C_{11} cycloalkylmethyl, C_6 to C_{10} aryl, or C_7 to
 C_{11} arylalkyl;

R^8 is selected from:

10 R^6 ;
 $\text{C}_1\text{-C}_{10}$ alkyl, substituted with 0-3 R^6 ;
 $\text{C}_2\text{-C}_{10}$ alkenyl, substituted with 0-3 R^6 ;
 $\text{C}_2\text{-C}_{10}$ alkynyl, substituted with 0-3 R^6 ;
 $\text{C}_3\text{-C}_8$ cycloalkyl, substituted with 0-3 R^6 ;
15 $\text{C}_5\text{-C}_6$ cycloalkenyl, substituted with 0-3 R^6 ;
aryl, substituted with 0-3 R^6 ;
5-10 membered heterocyclic ring containing 1-3 N,
O, or S heteroatoms, wherein said heterocyclic
ring may be saturated, partially saturated, or
20 fully unsaturated, said heterocyclic ring
being substituted with 0-2 R^6 ;

25 R^{12} and R^{13} are independently H, $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_1\text{-C}_{10}$
alkoxycarbonyl, $\text{C}_1\text{-C}_{10}$ alkylcarbonyl, $\text{C}_1\text{-C}_{10}$
alkylsulfonyl, aryl($\text{C}_1\text{-C}_{10}$ alkyl)sulfonyl,
arylsulfonyl, aryl($\text{C}_2\text{-C}_{10}$ alkenyl)sulfonyl,
heteroarylsulfonyl, aryl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_3\text{-C}_{11}$
cycloalkyl, $\text{C}_4\text{-C}_{11}$ cycloalkylalkyl, $\text{C}_7\text{-C}_{11}$
arylalkyl, $\text{C}_7\text{-C}_{11}$ arylcarbonyl, $\text{C}_4\text{-C}_{11}$
30 cycloalkoxycarbonyl, $\text{C}_7\text{-C}_{11}$ bicycloalkoxycarbonyl,
 $\text{C}_7\text{-C}_{11}$ aryloxycarbonyl, heteroarylcarbonyl,
heteroarylalkylcarbonyl, or
aryl($\text{C}_1\text{-C}_{10}$ alkoxy)carbonyl, wherein said aryls are
optionally substituted with 0-3 substituents

-26-

selected from the group consisting of: C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, CF₃, and NO₂;

5 R¹⁴ is selected from H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, aryl, heteroaryl or C₁-C₁₀ alkoxy carbonyl, CO₂R⁵ or -C(=O)N(R⁵)R^{5a};

10 R¹⁵ is selected from:
H; R⁶; -CO₂R⁵; -C(=O)N(R⁵)R^{5a};
C₁-C₁₀ alkoxy carbonyl substituted with 0-2 R⁶;
C₁-C₁₀ alkyl, substituted with 0-3 R⁶;
C₂-C₁₀ alkenyl, substituted with 0-3 R⁶;
C₁-C₁₀ alkoxy, substituted with 0-3 R⁶;

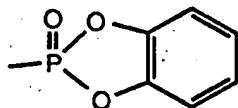
15 aryl, substituted with 0-3 R⁶; or
5-10 membered heterocyclic ring containing 1-3 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-2 R⁶;

20 provided that when b is a double bond, only one of R¹⁴ or R¹⁵ is present;

25 R¹⁶ is selected from:
-C(=O)-O-R^{18a},
-C(=O)-R^{18b},
-C(=O)N(R^{18b})₂,
-C(=O)NHSO₂R^{18a},
-C(=O)NHC(=O)R^{18b},
30 -C(=O)NHC(=O)OR^{18a},
-C(=O)NHSO₂NHR^{18b},
-C(=S)-NH-R^{18b},
-NH-C(=O)-O-R^{18a},
-NH-C(=O)-R^{18b},
35 -NH-C(=O)-NH-R^{18b},

-27-

- SO₂-O-R^{18a},
- SO₂-R^{18a},
- ~~-SO₂-N(18b)₂,~~
- SO₂-NHC(=O)O18b,
- 5 -P(=S)(OR^{18a})₂,
- P(=O)(OR^{18a})₂,
- P(=S)(R^{18a})₂,
- P(=O)(R^{18a})₂, or



10

R¹⁷ is selected from: H, C₁-C₁₀ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₅ cycloalkylalkyl, aryl, aryl(C₁-C₁₀ alkyl)-;

15 R^{18a} is selected from:

C₁-C₈ alkyl substituted with 0-2 R¹⁹,

C₂-C₈ alkenyl substituted with 0-2 R¹⁹,

C₂-C₈ alkynyl substituted with 0-2 R¹⁹,

C₃-C₈ cycloalkyl substituted with 0-2 R¹⁹,

20

aryl substituted with 0-4 R¹⁹,

aryl(C₁-C₆ alkyl)- substituted with 0-4 R¹⁹,

25

a 5-10 membered heterocyclic ring system having 1-3 heteroatoms selected independently from O, S, and N, said heterocyclic ring being substituted with 0-4 R¹⁹,

30

C₁-C₆ alkyl substituted with a 5-10 membered heterocyclic ring system having 1-3 heteroatoms selected independently from O, S, and N, said heterocyclic ring being substituted with 0-4 R¹⁹;

R^{18b} is selected from R^{18a} or H;

-28-

R^{19} is selected from H, halogen, CF_3 , CN , NO_2 , $NR^{12}R^{13}$, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylalkyl, aryl, aryl(C_1-C_6 alkyl)-, C_1-C_6 alkoxy, or C_1-C_4 alkoxy carbonyl;

5

m is 0-2;

n is 0-4;

q is 1-7;

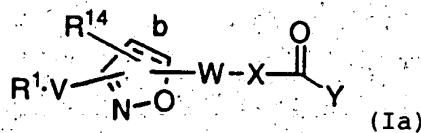
r is 0-3;

10

provided that n , q and r are chosen such that the number of atoms connecting R^1 and Y is in the range of 8-18.

15

[7] Preferred compounds of this second embodiment are those compounds of Formula Ia:



wherein:

20. Z is selected from a bond (i.e. is absent), O, or S;
and/or

R² is selected from H, aryl(C₁-C₁₀ alkoxy)carbonyl, or C₁-C₁₀ alkoxycarbonyl; and/or

25

W₁ is -(CH₂)₅C(=O)N(R^{5a}) and/or

X is $-(C(R^4)_2)_n-C(R^4)(R^8)-CH(R^4)-$, with the proviso that when n is 0 or 1, then at least one of R^4 or

30

R^8 is other than H or methyl; and/or

R^5 is selected from H or C_1-C_{10} alkyl substituted with 0-6 R^{4b} ; and/or

-29-

R^6 is selected from H, C₁-C₁₀ alkyl, hydroxy, C₁-C₁₀ alkoxy, nitro, C₁-C₁₀ alkylcarbonyl, -N(R¹²)R¹³, -NR⁵R^{5a}, CO₂R⁵, S(O)_mR⁵, OR⁵, cyano, halo;

5

C₆ to C₁₀ aryl optionally substituted with 1-3 groups selected from halogen, C₁-C₆ alkoxy, C₁-C₆ alkyl, CF₃, S(O)_mMe, or -NMe₂;

10

C₇ to C₁₁ arylalkyl, said aryl being optionally substituted with 1-3 groups selected from halogen, C₁-C₆ alkoxy, C₁-C₆ alkyl, CF₃, S(O)_mMe, or -NMe₂;

15

methylenedioxy when R^6 is a substituent on aryl; or

20

a 5-10 membered heterocyclic ring containing 1-3 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-2 R⁷; and/or

R⁷

is selected from selected from H, C₁-C₁₀ alkyl, hydroxy, C₁-C₁₀ alkoxy, nitro, C₁-C₁₀ alkylcarbonyl, -N(R¹²)R¹³, cyano, or halo; and/or

25

R⁸

is selected from:

-CONR⁵NR^{5a}; -CO₂R⁵;

C₁-C₁₀ alkyl, substituted with 0-3 R⁶;

C₂-C₁₀ alkenyl, substituted with 0-3 R⁶;

30

C₂-C₁₀ alkynyl, substituted with 0-3 R⁶,

C₃-C₈ cycloalkyl, substituted with 0-3 R⁶;

C₅-C₆ cycloalkenyl, substituted with 0-3 R⁶;

aryl, substituted with 0-2 R⁶;

5-10 membered heterocyclic ring containing 1-3 N,

35

O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or

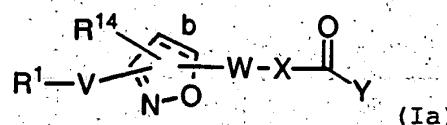
-30-

fully unsaturated, said heterocyclic ring
being substituted with 0-2 R⁶; and/or

R¹² and R¹³ are each independently selected from H,
5 C₁-C₁₀ alkyl, C₁-C₁₀ alkoxy carbonyl, C₁-C₁₀
alkyl carbonyl, C₁-C₁₀ alkylsulfonyl,
aryl (C₁-C₁₀ alkyl) sulfonyl, arylsulfonyl, aryl,
heteroaryl carbonyl, or heteroarylalkyl carbonyl,
wherein said aryls are optionally substituted with
10 0-3 substituents selected from the group consisting
of: C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, CF₃, and NO₂.

[8] Further preferred compounds of this second
embodiment are those compounds of Formula Ia:

15



wherein:

20 Z is selected from a bond (i.e. is absent) or O; and/or

W is -(CH₂)_nC(=O)N(R¹²)-; and/or

X is -C(R⁴)(R⁸)-C(R⁴)₂-.

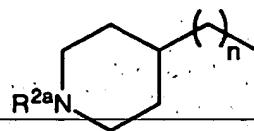
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[9] Further preferred compounds of this second
embodiment are compounds of Formula Ia, wherein:

R¹ is R²NHC(=NR²)- or R²NHC(=NR²)NH- and V is phenylene
30 or pyridylene, or

R¹ is

-31-



and V is a single bond (i.e. V

is absent);

n is 1 or 2;

5

X is -CHR<sup>8</sup>CH<sub>2</sub>;

Y is selected from:

hydroxy;

10 Ci to C<sub>10</sub> alkoxy;

methylcarbonyloxymethoxy-;

ethylcarbonyloxymethoxy-;

t-butylcarbonyloxymethoxy-;

cyclohexylcarbonyloxymethoxy-;

15 1-(methylcarbonyloxy)ethoxy-;

1-(ethylcarbonyloxy)ethoxy-;

1-(t-butylcarbonyloxy)ethoxy-;

1-(cyclohexylcarbonyloxy)ethoxy-;

i-propyloxycarbonyloxymethoxy-;

20 t-butyloxycarbonyloxymethoxy-;

1-(i-propyloxycarbonyloxy)ethoxy-;

1-(cyclohexyloxycarbonyloxy)ethoxy-;

1-(t-butyloxycarbonyloxy)ethoxy-;

dimethylaminoethoxy-;

25 diethylaminoethoxy-;

(5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;

(5-(t-butyl)-1,3-dioxacyclopenten-2-on-4-

y1)methoxy-;

(1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methoxy-;

30 1-(2-(2-methoxypropyl)carbonyloxy)ethoxy-;

-32-

R⁶ is selected from H, C₁-C₄ alkyl, hydroxy, C₁-C₄ alkoxy, nitro, C₁-C₁₀ alkylcarbonyl, -N(R¹²)R¹³, -NR⁵R^{5a}, CO₂R⁵, S(O)_mR⁵, OR⁵, cyano, halo;

5 C₆ to C₁₀ aryl optionally substituted with 1-3 groups selected from halogen, C₁-C₆ alkoxy, C₁-C₆ alkyl, CF₃, S(O)_mMe, or -NMe₂;

10 methylenedioxy when R⁶ is a substituent on aryl; or

15 a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, triazolyl, imidazolyl, benzofuranyl, indolyl, indolinyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3H-indolyl, carbazolyl, pyrrolidinyl, piperidinyl, indolinyl, isoxazolinyl or morpholinyl;

20 R⁸ is selected from:

-CONR⁵NR^{5a}; -CO₂R⁵;
C₁-C₁₀ alkyl, substituted with 0-3 R⁶;
C₂-C₁₀ alkenyl, substituted with 0-3 R⁶;
25 C₂-C₁₀ alkynyl, substituted with 0-3 R⁶;
C₃-C₈ cycloalkyl, substituted with 0-3 R⁶;
aryl, substituted with 0-2 R⁶;

30 a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, triazolyl, imidazolyl, benzofuranyl, indolyl, indolinyl, quinolinyl, isoquinolinyl, isoxazolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3H-indolyl, carbazolyl, pyrrolidinyl, piperidinyl, indolinyl, or

35

-33-

morpholinyl, said heterocyclic ring being substituted with 0-2 R⁶;

R¹² is selected from H, C₁-C₆ alkyl, C₁-C₄ alkoxy carbonyl, C₁-C₆ alkyl carbonyl, C₁-C₆ alkylsulfonyl, aryl(C₁-C₄ alkyl)sulfonyl, arylsulfonyl, aryl, pyridyl carbonyl or pyridylmethyl carbonyl, wherein said aryls are optionally substituted with 0-3 substituents selected from the group consisting of: C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, CF₃, and NO₂; and

R¹³ is H.

[10] Specifically preferred compounds of this second embodiment are compounds, or pharmaceutically acceptable salt or prodrug forms thereof, selected from:

3 (R, S)-{5 (R, S)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-3-phenylpropanoic acid;
3 (R, S)-{5 (R, S)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-pentanoic acid;
3 (R)-{5 (R, S)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}heptanoic acid;
3 (R, S)-{5 (R, S)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-4-(phenylthio)butanoic acid;
3 (R, S)-{5 (R, S)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-4-(phenylsulfonamido)butanoic acid;
3 (R, S)-{5 (R, S)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-4-(n-butylsulfonamido)butanoic acid;
3 (S)-{5 (R, S)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-3-(adamantylmethylaminocarbonyl)propanoic acid;

-34-

3 (S)-{5 (R, S)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-3-(1-azabicyclo[3.2.2]nonylcarbonyl)propanoic acid;

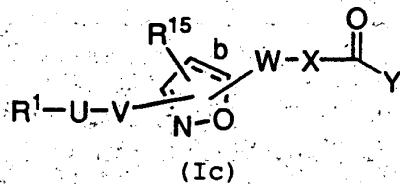
3 (S)-{5 (R, S)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-3-(phenethylaminocarbonyl)propanoic acid;

3 (R)-{5 (R, S)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-3-(3-pyridylethyl)propanoic acid.

3 (R)-{5 (R, S)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-3-(2-pyridylethyl)propanoic acid.

3 (R)-{5 (R, S)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-3-(phenylpropyl)propanoic acid.

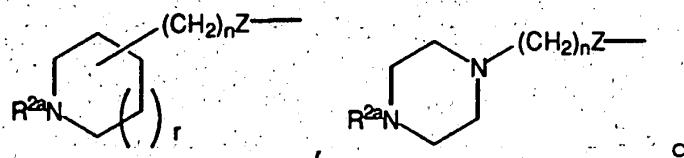
[11] Also preferred compounds of the second embodiment are those compounds of Formula Ic:



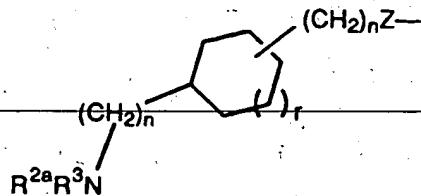
20 wherein:

b is a single or double bond;

R¹ is selected from R²a(R³)N-, R²(R³)N(R²N=)C-,
 R²a(R³)N(CH₂)ₗZ-, R²(R³)N(R²N=)C(CH₂)ₗZ-,
 25 R²(R³)N(R²N=)CN(R²)-,



-35-



Z is selected from a bond (i.e. is absent), O, or S;

5. R² and R³ are independently selected from H, aryl(C₁-C₁₀ alkoxy)carbonyl, or C₁-C₁₀ alkoxycarbonyl;

R^{2a} is R² or R²(R³)N(R²N=)C;

10. U is a single bond (i.e., U is not present),

V is selected from:

a single bond (i.e., V is not present);

-(C₁-C₇ alkyl)-, substituted with 0-3 groups

15 independently selected from R⁶ or R⁷;

-(C₂-C₇ alkenyl)-, substituted with 0-3 groups

independently selected from R⁶ or R⁷;

-(C₂-C₇ alkynyl)-, substituted with 0-3 groups

independently selected from R⁶ or R⁷;

20 -(phenyl)-Q-, said phenyl substituted with 0-2 groups independently selected from R⁶ or R⁷;

-(pyridyl)-Q-, said pyridyl substituted with 0-2

groups independently selected from R⁶ or R⁷; or

25 -(pyridazinyl)-Q-, said pyridazinyl substituted

with 0-2 groups independently selected from R⁶ or R⁷.

Q is selected from

a single bond (i.e., Q is not present),

30 -O-, -S(O)_m-, -N(R¹²)-, -(CH₂)_m-, -C(=O)-,

-N(R^{5a})C(=O)-, -C(=O)N(R^{5a})-, -CH₂O-, -OCH₂-,

-36-

$-\text{CH}_2\text{N}(\text{R}^{12})-$, $-\text{N}(\text{R}^{12})\text{CH}_2-$, $-\text{CH}_2\text{C}(=\text{O})-$, $-\text{C}(=\text{O})\text{CH}_2-$,
 $-\text{CH}_2\text{S}(\text{O})_m-$, or $-\text{S}(\text{O})_m\text{CH}_2-$,

provided that when b is a single bond, and $\text{R}^1\text{--U--V--}$
5 is a substituent on C5 of the central 5-membered
ring in Formula I, then Q is not $-\text{O}-$, $-\text{S}(\text{O})_m-$,
 $-\text{N}(\text{R}^{12})-$, $-\text{C}(=\text{O})\text{N}(\text{R}^{5a})-$, $-\text{CH}_2\text{O}-$, $\text{CH}_2\text{N}(\text{R}^{12})-$ or
 $-\text{CH}_2\text{S}(\text{O})_m-$;

10 W is selected from:

$-(\text{C}(\text{R}^4)_2)\text{--C}(=\text{O})\text{--N}(\text{R}^{5a})-$, or
 $-\text{C}(=\text{O})\text{--N}(\text{R}^{5a})\text{--}(\text{C}(\text{R}^4)_2)-$;

X is $-\text{C}(\text{R}^4)_2\text{--CHR}^{4a}-$;

15

R^4 is selected from H, $\text{C}_1\text{--C}_{10}$ alkyl, $\text{C}_1\text{--C}_{10}$
alkylcarbonyl, aryl, arylalkyl, cycloalkyl, or
cycloalkylalkyl;

20 R^{4a} is selected from hydroxy, $\text{C}_1\text{--C}_{10}$ alkoxy, nitro,
 $-\text{N}(\text{R}^5)\text{R}^{5a}$, $-\text{N}(\text{R}^{12})\text{R}^{13}$, or $-\text{N}(\text{R}^{16})\text{R}^{17}$,
 $\text{C}_1\text{--C}_{10}$ alkyl substituted with 0-3 R^6 ,
aryl substituted with 0-3 R^6 ,
heteroaryl substituted with 0-3 R^6 , or
25 $\text{C}_1\text{--C}_{10}$ alkylcarbonyl;

30 R^{4b} is selected from H, $\text{C}_1\text{--C}_6$ alkyl, $\text{C}_2\text{--C}_6$ alkenyl, $\text{C}_2\text{--}$
 C_6 alkynyl, hydroxy, $\text{C}_1\text{--C}_6$ alkoxy, $\text{C}_1\text{--C}_6$ alkylthio,
 $\text{C}_1\text{--C}_6$ alkylsulfinyl, $\text{C}_1\text{--C}_6$ alkylsulfonyl, nitro,
 $\text{C}_1\text{--C}_6$ alkylcarbonyl, $\text{C}_6\text{--C}_{10}$ aryl, $-\text{N}(\text{R}^{12})\text{R}^{13}$, halo,
 CF_3 , CN , $\text{C}_1\text{--C}_6$ alkoxycarbonyl, carboxy, piperidinyl,
morpholinyl or pyridyl;

35 R^5 is selected from H or $\text{C}_1\text{--C}_{10}$ alkyl substituted with
0-6 R^{4b} ;

5 R^{5a} is selected from hydrogen, hydroxy, C₁ to C₈ alkyl, C₂ to C₆ alkenyl, C₃ to C₁₁ cycloalkyl, C₄ to C₁₁ cycloalkylmethyl, C₁-C₆ alkoxy, benzyloxy, C₆ to C₁₀ aryl, heteroaryl, heteroarylalkyl, C₇ to C₁₁ arylalkyl, or adamantylmethyl, C₁-C₁₀ alkyl substituted with 0-2 R^{4b};

10 alternately, R⁵ and R^{5a} can be taken together to be 3-azabicyclononyl, 1,2,3,4-tetrahydro-1-quinolinyl, 1,2,3,4-tetrahydro-2-isoquinolinyl, 1-piperidinyl, 1-morpholinyl, 1-pyrrolidinyl, thiamorpholinyl, thiazolidinyl or 1-piperazinyl, each being optionally substituted with C₁-C₆ alkyl, C₆-C₁₀ aryl, heteroaryl, C₇-C₁₁ arylalkyl, C₁-C₆ alkylcarbonyl, C₃-C₇ cycloalkylcarbonyl, C₁-C₆ alkoxy carbonyl or C₇-C₁₁ arylalkoxycarbonyl;

15 R^{5b} is selected from C₁-C₈ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylmethyl, C₆-C₁₀ aryl, C₇-C₁₁ arylalkyl, or C₁-C₁₀ alkyl substituted with 0-2 R^{4b}

20 Y is selected from hydroxy, C₁ to C₁₀ alkyloxy, C₃ to C₁₁ cycloalkyloxy, C₆ to C₁₀ aryloxy, C₇ to C₁₁ aralkyloxy, C₃ to C₁₀ alkylcarbonyloxyalkyloxy, C₃ to C₁₀ alkoxy carbonyloxyalkyloxy, C₂ to C₁₀ alkoxy carbonylalkyloxy, C₅ to C₁₀ cycloalkylcarbonyloxyalkyloxy, C₅ to C₁₀ cycloalkoxycarbonyloxyalkyloxy, C₅ to C₁₀ cycloalkoxycarbonylalkyloxy, C₇ to C₁₁ aryloxy carbonylalkyloxy, C₈ to C₁₂ aryloxy carbonyloxyalkyloxy, C₈ to C₁₂ arylcarbonyloxyalkyloxy, C₅ to C₁₀ alkoxy alkylcarbonyloxyalkyloxy, C₅ to C₁₀ (5-alkyl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy, or C₁₀ to

-38-

C₁₄ (5-aryl-1,3-dioxa-cyclopenten-2-one-
y1)methoxy;

R⁶ and R⁷ are each independently selected from H, C₁-C₁₀
5 alkyl, hydroxy, C₁-C₁₀ alkoxy, nitro, C₁-C₁₀
alkylcarbonyl, -N(R¹²)R¹³, cyano, or halo;

R¹² and R¹³ are each independently selected from H,
10 C₁-C₁₀ alkyl, C₁-C₁₀ alkoxy carbonyl, C₁-C₁₀
alkylcarbonyl, C₁-C₁₀ alkylsulfonyl,
aryl(C₁-C₁₀ alkyl)sulfonyl, arylsulfonyl,
heteroaryl carbonyl, heteroarylalkylcarbonyl or
15 aryl, wherein said aryls are optionally substituted
with 0-3 substituents selected from the group
consisting of: C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, CF₃,
and NO₂;

R¹⁵ is selected from H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl,
20 C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, aryl, heteroaryl or
C₁-C₁₀ alkoxy carbonyl, CO₂R⁵ or -C(=O)N(R⁵)R^{5a};

R¹⁶ is selected from:
-C(=O)-O-R^{18a},
-C(=O)-R^{18b},
25 -C(=O)N(R^{18b})₂,
-SO₂-R^{18a}, or
-SO₂-N(R^{18b})₂;

R¹⁷ is selected from: H or C₁-C₄ alkyl;

30 R^{18a} is selected from:
C₁-C₈ alkyl substituted with 0-2 R¹⁹,
C₂-C₈ alkenyl substituted with 0-2 R¹⁹,
C₂-C₈ alkynyl substituted with 0-2 R¹⁹,
35 C₃-C₈ cycloalkyl substituted with 0-2 R¹⁹,

-39-

aryl substituted with 0-4 R¹⁹,
aryl(C₁-C₆ alkyl)- substituted with 0-4 R¹⁹,

5 a heterocyclic ring system selected from pyridinyl,
furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl,
triazolyl, imidazolyl, benzofuranyl, indolyl,
indolinyl, quinolinyl, isoquinolinyl, isoxazolinyl,
benzimidazolyl, piperidinyl, tetrahydrofuranol,
10 pyranol, pyrimidinyl, 3H-indolyl, carbazolyl,
pyrrolidinyl, piperidinyl, indolinyl, or
morpholinyl, said heterocyclic ring being
substituted with 0-4 R¹⁹;

15 C₁-C₆ alkyl substituted with a heterocyclic ring
system selected from pyridinyl, furanyl, thiazolyl,
thienyl, pyrrolyl, pyrazolyl, imidazolyl,
isoxazolinyl, benzofuranyl, indolyl, indolenyl,
quinolinyl, isoquinolinyl, benzimidazolyl,
piperidinyl, tetrahydrofuranol, pyranol, pyridinyl,
20 3H-indolyl, indolyl, carbazole, pyrrolidinyl,
piperidinyl, indolinyl, or morpholinyl, said
heterocyclic ring being substituted with 0-4 R¹⁹;

25 R^{18b} is selected from R^{18a} or H;

30 R¹⁹ is selected from H, halogen, CF₃, CN, NO₂, NR¹²R¹³,
C₁-C₈ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆
alkoxy, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl,
aryl, heteroaryl, aryl(C₁-C₆ alkyl)-, or C₁-C₄
alkoxycarbonyl;

n is 0-4;

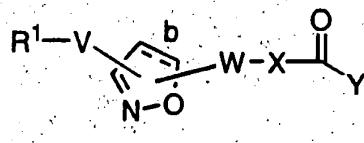
q is 1-7;

r is 0-3;

-40-

provided that n, q, and r are chosen such that the number of atoms between R^1 and Y is in the range of 8-17.

5 [12] Further preferred compounds of the second embodiment of Formula Ic are those compounds of Formula Ib:



10

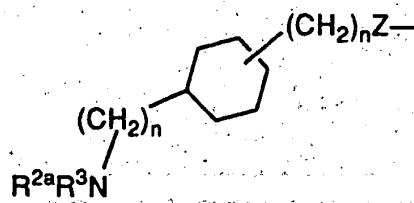
(Ib)

wherein:

15 R^1 is selected from: $R^2(R^3)N-$, $R^2NH(R^2N=)C-$,
 $R^2NH(R^2N=)CNH-$, $R^2R^3N(CH_2)_{p'}Z-$,
 $R^2NH(R^2N=)CNH(CH_2)_{p''}Z-$ or



or



20

n is 0-1;

p' is 4-6;

p'' is 2-4;

25

Z is selected from a bond (i.e. is absent) or O;

-41-

V is a single bond (i.e., V is not present),
-(phenyl)- or -(pyridyl)-;

W is selected from:

5 -(C(R⁴)₂)-C(=O)-N(R^{5a})-,
-C(=O)-N(R^{5a})-CH₂-;

X is selected from:

10 -CH₂-CHN(R¹⁶)R¹⁷-, or
-CH₂-CHNR⁵R^{5a}-;

Y is selected from:

hydroxy;
C₁ to C₁₀ alkoxy;
15 methylcarbonyloxymethoxy-;
ethylcarbonyloxymethoxy-;
t-butylcarbonyloxymethoxy-;
cyclohexylcarbonyloxymethoxy-;
1-(methylcarbonyloxy)ethoxy-;
20 1-(ethylcarbonyloxy)ethoxy-;
1-(t-butylcarbonyloxy)ethoxy-;
1-(cyclohexylcarbonyloxy)ethoxy-;
i-propyloxycarbonyloxymethoxy-;
t-butyloxycarbonyloxymethoxy-;
25 1-(i-propyloxycarbonyloxy)ethoxy-;
1-(cyclohexyloxycarbonyloxy)ethoxy-;
1-(t-butyloxycarbonyloxy)ethoxy-;
dimethylaminoethoxy-;
diethylaminoethoxy-;
30 (5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;
(5-(t-butyl)-1,3-dioxacyclopenten-2-on-4-
yl)methoxy-;
(1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methoxy-;
1-(2-(2-methoxypropyl)carbonyloxy)ethoxy-;

35

R¹⁶ is selected from:

-42-

-C(=O)-O-R^{18a},
-C(=O)-R^{18b},
-S(=O)₂-R^{18a} or
-SO₂-N(R^{18b})₂;

5

R¹⁷ is selected from H or C₁-C₅ alkyl;

R^{18a} is selected from:

10 C₁-C₈ alkyl substituted with 0-2 R¹⁹,
C₂-C₈ alkenyl substituted with 0-2 R¹⁹,
C₂-C₈ alkynyl substituted with 0-2 R¹⁹,
C₃-C₈ cycloalkyl substituted with 0-2 R¹⁹,
aryl substituted with 0-4 R¹⁹,
aryl(C₁-C₆ alkyl)- substituted with 0-4 R¹⁹,

15

a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, triazolyl, imidazolyl, benzofuranyl, indolyl, indolinyl, quinolinyl, isoquinolinyl, isoxazolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyrimidinyl, 3H-indolyl, carbazolyl, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-4 R¹⁹;

25

C₁-C₆ alkyl substituted with a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolinyl, benzofuranyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3H-indolyl, indolyl, carbazole, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-4 R¹⁹.

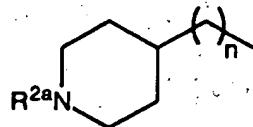
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-43-

[13] Further preferred compounds of Formula Ib are those compounds wherein:

5 R¹ is R²NH(R²N=)C- or R²HN(R²N=)CNH- and V is phenylene or pyridylene; or

10 R¹ is



and V is a single bond (i.e. V is absent);

15

n is 1 or 2;

R^{18a} is selected from:

C₁-C₄ alkyl substituted with 0-2 R¹⁹,

15 C₂-C₄ alkenyl substituted with 0-2 R¹⁹,

C₂-C₄ alkynyl substituted with 0-2 R¹⁹,

C₃-C₇ cycloalkyl substituted with 0-2 R¹⁹,

aryl substituted with 0-4 R¹⁹,

aryl(C₁-C₄ alkyl)- substituted with 0-4 R¹⁹,

20

a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, triazolyl, imidazolyl, benzofuranyl, indolyl, indolinyl, quinolinyl, isoquinolinyl, isoxazolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyrimidinyl, 3H-indolyl, carbazolyl, pyrrolidinyl, piperidinyl, indolinyl, isoxazolinyl or morpholinyl, said heterocyclic ring being substituted with 0-4 R¹⁹;

25

C₁-C₄ alkyl substituted with a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl,

30

-44-

isoxazoliny1, benzofuranyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuran1, pyranyl, pyridinyl, 3H-indolyl, indolyl, carbazole, pyrrolidinyl, 5 piperidinyl, indolinyl, isoxazolinyl or morpholinyl, said heterocyclic ring being substituted with 0-4 R¹⁹.

[14] Specifically preferred compounds of Formula Ib are compounds, or pharmaceutically acceptable salt forms thereof, selected from:

15 $N^3-[2-\{3-(4\text{-formamidinophenyl})\text{-isoxazolin-5}(R,S)\text{-yl}\}\text{-acetyl}]\text{-N}2\text{-}(\text{phenylsulfonyl})\text{-2,3-(S)-diaminopropanoic acid;}$

20 $N^3-[2-\{3-(4\text{-formamidinophenyl})\text{-isoxazolin-5}(R,S)\text{-yl}\}\text{-acetyl}]\text{-N}2\text{-}(4\text{-methyl-phenyl-sulfonyl})\text{-2,3-(S)-diaminopropanoic acid;}$

25 $N^3-[2-\{3-(4\text{-formamidinophenyl})\text{-isoxazolin-5}(R,S)\text{-yl}\}\text{-acetyl}]\text{-N}2\text{-}(\text{butanesulfonyl})\text{-2,3-(S)-diaminopropanoic acid;}$

30 $N^3-[2-\{3-(4\text{-formamidinophenyl})\text{-isoxazolin-5}(R,S)\text{-yl}\}\text{-acetyl}]\text{-N}2\text{-}(\text{propanesulfonyl})\text{-2,3-(S)-diaminopropanoic acid;}$

35 $N^3-[2-\{3-(4\text{-formamidinophenyl})\text{-isoxazolin-5}(R,S)\text{-yl}\}\text{-acetyl}]\text{-N}2\text{-}(\text{ethanesulfonyl})\text{-2,3-(S)-diaminopropanoic acid;}$

40 $N^3-[2-\{3-(4\text{-formamidinophenyl})\text{-isoxazolin-5}(R,S)\text{-yl}\}\text{-acetyl}]\text{-N}2\text{-}(\text{methyloxycarbonyl})\text{-2,3-(S)-diaminopropanoic acid;}$

45 $N^3-[2-\{3-(4\text{-formamidinophenyl})\text{-isoxazolin-5}(R,S)\text{-yl}\}\text{-acetyl}]\text{-N}2\text{-}(\text{ethyloxycarbonyl})\text{-2,3-(S)-diaminopropanoic acid;}$

15 $N^3-[2-\{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl\}-$
acetyl]-N2-(1-propyloxycarbonyl)-2,3-(S)-
diaminopropanoic acid;

20 $N^3-[2-\{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl\}-$
acetyl]-N2-(2-propyloxycarbonyl)-2,3-(S)-
diaminopropanoic acid;

25 $N^3-[2-\{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl\}-$
acetyl]-N2-(n-butyloxycarbonyl)-2,3-(S)-
diaminopropanoic acid;

30 $N^3-[2-\{3-(4-formamidinophenyl)-isoxazolin-5(R)-yl\}-$
acetyl]-N2-(n-butyloxycarbonyl)-2,3-(S)-
diaminopropanoic acid;

35 $N^3-[2-\{3-(4-formamidinophenyl)-isoxazolin-5(S)-yl\}-$
acetyl]-N2-(n-butyloxycarbonyl)-2,3-(S)-
diaminopropanoic acid;

40 $N^3-[2-\{3-(4-formamidinophenyl)-isoxazolin-5(R)-yl\}-$
acetyl]-N2-(n-butyloxycarbonyl)-2,3-(R)-
diaminopropanoic acid;

45 $N^3-[2-\{3-(4-formamidinophenyl)-isoxazolin-5(S)-yl\}-$
acetyl]-N2-(n-butyloxycarbonyl)-2,3-(R)-
diaminopropanoic acid;

50 $N^3-[2-\{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl\}-$
acetyl]-N2-(2-butyloxycarbonyl)-2,3-(S)-
diaminopropanoic acid;

55 $N^3-[2-\{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl\}-$
acetyl]-N2-(1-(2-methyl)-propyloxycarbonyl)-2,3-(S)-
diaminopropanoic acid;

60 $N^3-[2-\{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl\}-$
acetyl]-N2-(2-(2-methyl)-propyloxycarbonyl)-2,3-(S)-
diaminopropanoic acid;

65 $N^3-[2-\{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl\}-$
acetyl]-N2-(benzyloxycarbonyl)-2,3-(S)-
diaminopropanoic acid;

5 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R*)-yl}-
 acetyl]-N2-(benzyloxycarbonyl)-2,3-(*S*)-
 diaminopropanoic acid;

10 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(*S*)-yl}-
 acetyl]-N2-(benzyloxycarbonyl)-2,3-(*S*)-
 diaminopropanoic acid;

15 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-
 acetyl]-N2-(4-methylbenzyloxycarbonyl)-2,3-(*S*)-
 diaminopropanoic acid;

20 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-
 acetyl]-N2-(4-methoxybenzyloxycarbonyl)-2,3-(*S*)-
 diaminopropanoic acid;

25 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-
 acetyl]-N2-(4-chlorobenzylloxycarbonyl)-2,3-(*S*)-
 diaminopropanoic acid;

30 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-
 acetyl]-N2-(4-bromobenzylloxycarbonyl)-2,3-(*S*)-
 diaminopropanoic acid;

35 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-
 acetyl]-N2-(4-fluorobenzylloxycarbonyl)-2,3-(*S*)-
 diaminopropanoic acid;

40 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-
 acetyl]-N2-(4-phenoxybenzyloxycarbonyl)-2,3-(*S*)-
 diaminopropanoic acid;

45 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-
 acetyl]-N2-(2-(methyloxyethyl)-oxycarbonyl)-2,3-(*S*)-
 diaminopropanoic acid;

50 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-
 acetyl]-N2-(2-pyridinylcarbonyl)-2,3-(*S*)-
 diaminopropanoic acid;

55 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-
 acetyl]-N2-(3-pyridinylcarbonyl)-2,3-(*S*)-
 diaminopropanoic acid;

N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-
5 acetyl]-N2-(4-pyridinyl-carbonyl)-2,3-(S)-
diaminopropanoic acid;

N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-
10 acetyl]-N2-(2-(2-pyridinyl)-acetyl)-2,3-(S)-
diaminopropanoic acid;

N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-
15 acetyl]-N2-(2-(3-pyridinyl)-acetyl)-2,3-(S)-
diaminopropanoic acid;

N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-
20 acetyl]-N2-(2-(4-pyridinyl)-acetyl)-2,3-(S)-
diaminopropanoic acid;

N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-
25 acetyl]-N2-(2-pyridyl-methyloxycarbonyl)-2,3-(S)-
diaminopropanoic acid;

N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-
30 acetyl]-N2-(3-pyridyl-methyloxycarbonyl)-2,3-(S)-
diaminopropanoic acid.

N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-
35 acetyl]-N2-(4-butyloxyphenylsulfonyl)-2,3-(S)-
diaminopropanoic acid;

N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-
40 acetyl]-N2-(2-thienylsulfonyl)-2,3-(S)-
diaminopropanoic acid;

N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-
45 acetyl]-N2-(3-methylphenylsulfonyl)-2,3-(R,S)-
diaminopropanoic acid;

N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-
50 acetyl]-N2-(3-methylphenylsulfonyl)-2,3-(S)-
diaminopropanoic acid;

5 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-
 acetyl]-N2-(3-methylphenylsulfonyl)-2,3-(R)-
 diaminopropanoic acid;

10 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(R)-yl}-
 acetyl]-N2-(3-methylphenylsulfonyl)-2,3-(S)-
 diaminopropanoic acid;

15 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(S)-yl}-
 acetyl]-N2-(3-methylphenylsulfonyl)-2,3-(S)-
 diaminopropanoic acid;

20 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(R)-yl}-
 acetyl]-N2-(3-methylphenylsulfonyl)-2,3-(R)-
 diaminopropanoic acid;

25 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-
 acetyl]-N2-(3-trifluoromethylphenylsulfonyl)-2,3-
 (S)-diaminopropanoic acid;

30 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-
 acetyl]-N2-(3-chlorophenylsulfonyl)-2,3-(S)-
 diaminopropanoic acid;

35 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-
 acetyl]-N2-(3-2-methoxycarbonylphenylsulfonyl)-2,3-
 (S)-diaminopropanoic acid;

40 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-
 acetyl]-N2-(2,4,6-trimethylphenylsulfonyl)-2,3-(S)-
 diaminopropanoic acid;

45 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-
 acetyl]-N2-(2-chlorophenylsulfonyl)-2,3-(S)-
 diaminopropanoic acid;

-49-

5 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-
 acetyl]-N2-(4-trifluoromethylphenylsulfonyl)-2,3-
 (S)-diaminopropanoic acid;

10 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-
 acetyl]-N2-(2-trifluoromethylphenylsulfonyl)-2,3-
 (S)-diaminopropanoic acid;

15 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-
 acetyl]-N2-(2-fluorophenylsulfonyl)-2,3-(S)-
 diaminopropanoic acid;

20 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-
 acetyl]-N2-(4-fluorophenylsulfonyl)-2,3-(S)-
 diaminopropanoic acid;

25 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-
 acetyl]-N2-(4-methoxyphenylsulfonyl)-2,3-(S)-
 diaminopropanoic acid;

30 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-
 acetyl]-N2-(2,3,5,6-tetramethylphenylsulfonyl)-2,3-
 (S)-diaminopropanoic acid;

35 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-
 acetyl]-N2-(4-cyanophenylsulfonyl)-2,3-(S)-
 diaminopropanoic acid;

40 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-
 acetyl]-N2-(4-chlorophenylsulfonyl)-2,3-(S)-
 diaminopropanoic acid;

45 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-
 acetyl]-N2-(4-propylphenylsulfonyl)-2,3-(S)-
 diaminopropanoic acid;

50 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-
 acetyl]-N2-(2-phenylethylsulfonyl)-2,3-(S)-
 diaminopropanoic acid;

55 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-
 acetyl]-N2-(4-isopropylphenylsulfonyl)-2,3-(S)-
 diaminopropanoic acid;

-50-

5 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-
 acetyl]-N2-(3-phenylpropylsulfonyl)-2,3-(S)-
 diaminopropanoic acid;

10 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-
 acetyl]-N2-(3-pyridylsulfonyl)-2,3-(S)-
 diaminopropanoic acid;

15 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-
 acetyl]-N2-(phenylaminosulfonyl)-2,3-(S)-
 diaminopropanoic acid;

20 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-
 acetyl]-N2-(benzylaminosulfonyl)-2,3-(S)-
 diaminopropanoic acid;

25 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-
 acetyl]-N2-(dimethylaminosulfonyl)-2,3-(S)-
 diaminopropanoic acid,

30 N^3 -[2-{3-(2-fluoro-4-formamidinophenyl)-isoxazolin-5(R,S)-
 yl}-acetyl]-N2-(3-methylphenylsulfonyl)-2,3-(S)-
 (S)-diaminopropanoic acid,

35 N^3 -[2-{3-(2-formamidino-5-pyridinyl)-isoxazolin-5(R,S)-
 yl}-acetyl]-N2-(n-butyloxycarbonyl)-2,3-(S)-
 diaminopropanoic acid,

40 N^3 -[2-{3-(2-formamidino-5-pyridinyl)-isoxazolin-5(R,S)-
 yl}-acetyl]-N2-(3-methylphenylsulfonyl)-2,3-(S)-
 diaminopropanoic acid,

45 N^3 -[2-{3-(3-formamidino-6-pyridinyl)-isoxazolin-5(R,S)-
 yl}-acetyl]-N2-(n-butyloxycarbonyl)-2,3-(S)-
 diaminopropanoic acid,

50 N^3 -[2-{3-(3-formamidino-6-pyridinyl)-isoxazolin-5(R,S)-
 yl}-acetyl]-N2-(3-methylphenylsulfonyl)-2,3-(S)-
 diaminopropanoic acid,

55 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-
 acetyl]-N2-(phenylaminocarbonyl)-2,3-(S)-
 diaminopropanoic acid;

-51-

N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-acetyl]-N2-(4-fluorophenylaminocarbonyl)-2,3-(S)-diaminopropanoic acid;

5 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-acetyl]-N2-(1-naphthylaminocarbonyl)-2,3-(S)-diaminopropanoic acid;

10 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-acetyl]-N2-(benzylaminocarbonyl)-2,3-(S)-diaminopropanoic acid;

15 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-acetyl]-N2-(3-bromo-2-thienylsulfonyl)-2,3-(S)-diaminopropanoic acid;

20 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-acetyl]-N2-(3-methyl-2-benzothienylsulfonyl)-2,3-(S)-diaminopropanoic acid,

25 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(R)-yl}-acetyl]-N2-(isobutyloxycarbonyl)-2,3-(S)-diaminopropanoic acid,

30 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(S)-yl}-acetyl]-N2-(isobutyloxycarbonyl)-2,3-(S)-diaminopropanoic acid,

35 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-acetyl]-N2-(2-cyclopropylethoxycarbonyl)-2,3-(S)-diaminopropanoic acid,

40 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(R)-yl}-acetyl]-N2-(2-cyclopropylethoxycarbonyl)-2,3-(S)-diaminopropanoic acid, and

45 N^3 -[2-{3-(4-formamidinophenyl)-isoxazolin-5(S)-yl}-acetyl]-N2-(2-cyclopropylethoxycarbonyl)-2,3-(S)-diaminopropanoic acid.

-52-

15 N^3 -[2-(3-(4-guanidinophenyl)-isoxazolin-5(R,S)-yl)-acetyl]-N2-(n-butyloxycarbonyl)-2,3-(S)-diaminopropanoic acid.

20 5 N^3 -[2-(3-(4-guanidinophenyl)-isoxazolin-5(R)-yl)-acetyl]-N2-(n-butyloxycarbonyl)-2,3-(S)-diaminopropanoic acid.

25 10 N^3 -[2-(3-(4-guanidinophenyl)-isoxazolin-5(R)-yl)-acetyl]-N2-(3-methylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid.

30 15 N^3 -[2-(5-(4-formamidinophenyl)-isoxazolin-3(R,S)-yl)-acetyl]-N2-(n-butyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

[15] 15 Also specifically preferred are prodrug esters of the specifically preferred compounds of Formula Ib, said esters being chosen from the group consisting of:

20 methyl;
ethyl;
isopropyl;
methylcarbonyloxymethyl-;
ethylcarbonyloxymethyl-;
t-butylcarbonyloxymethyl-;
cyclohexylcarbonyloxymethyl-;
1-(methylcarbonyloxy)ethyl-;
25 25 1-(ethylcarbonyloxy)ethyl-;
1-(t-butylcarbonyloxy)ethyl-;
1-(cyclohexylcarbonyloxy)ethyl-;
i-propyloxycarbonyloxymethyl-;
cyclohexylcarbonyloxymethyl-;
30 30 t-butyloxycarbonyloxymethyl-;
1-(i-propyloxycarbonyloxy)ethyl-;
1-(cyclohexyloxycarbonyloxy)ethyl-;
1-(t-butyloxycarbonyloxy)ethyl-;
dimethylaminoethyl-;
35 35 diethylaminoethyl-;

-53-

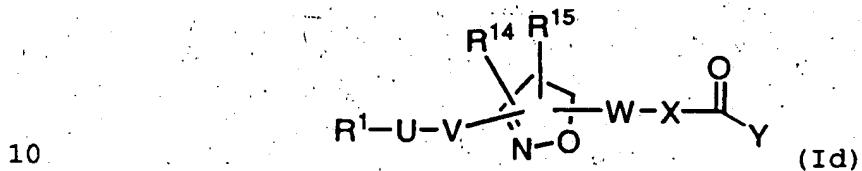
(5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methyl-;

(5-(t-butyl)-1,3-dioxacyclopenten-2-on-
4-yl)methyl-;

(1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methyl-;

5 1-(2-(2-methoxypropyl)carbonyloxy)ethyl-.

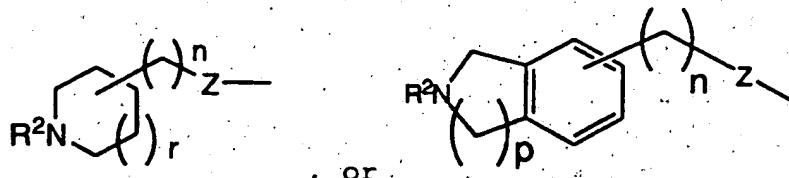
[16] A third embodiment of this invention provides a compound of Formula Id:



or a pharmaceutically acceptable salt or prodrug form thereof wherein:

15 R^1 is selected from is selected from $R^2(R^3)N-$, $R^2(R^3)N(R^2N=)C-$, $R^2(R^3)N(R^2N=)CN(R^2)-$, $R^2(R^3)N(CH_2)_qZ-$, $R^2(R^3)N(R^2N=)C(CH_2)_qZ-$, $R^2(R^3)N(R^2N=)CN(R^2)(CH_2)_qZ-$, piperazinyl- $(CH_2)_qZ-$, or

20



Z is selected from a bond (i.e., is absent), O, S, $S(=O)$, or $S(=O)_2$;

25 R^2 and R^3 are independently selected from: H, C₁-C₁₀ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, C₆-C₁₀ aryl, C₇-C₁₁ arylalkyl, C₂-C₇ alkylcarbonyl, C₇-C₁₁ arylcarbonyl, C₂-C₁₀ alkoxy carbonyl, C₄-C₁₁ cycloalkoxycarbonyl, C₇-C₁₁ bicycloalkoxycarbonyl, C₇-C₁₁ aryloxycarbonyl, or

-54-

aryl (C₁-C₁₀ alkoxy) carbonyl, C₁-C₆
alkylcarbonyloxy (C₁-C₄ alkoxy) carbonyl, C₆-C₁₀
arylcarbonyloxy (C₁-C₄ alkoxy) carbonyl, C₄-C₁₁
cycloalkylcarbonyloxy (C₁-C₄ alkoxy) carbonyl;

5.

U is selected from:

a single bond (i.e., U is absent)

C₁-C₇ alkylene,

C₂-C₇ alkenylene,

10

C₂-C₇ alkynylene,

arylene substituted with 0-3 R^{6a}, or

pyridylene substituted with 0-3 R^{6a};

V is selected from:

15

a single bond (i.e., V is absent);

C₁-C₇ alkylene substituted with 0-6 R⁶ or R⁷;

C₂-C₇ alkenylene substituted with 0-4 R⁶ or R⁷;

C₂-C₇ alkynylene substituted with 0-4 R⁶ or R⁷;

phenylene substituted with 0-4 R⁶ or R⁷;

20

pyridylene substituted with 0-3 R⁶ or R⁷;

pyridazinylene substituted with 0-3 R⁶ or R⁷;

X is selected from:

a single bond (i.e., X is absent);

25.

-(CH₂)_nC(=O)N(R¹²)-;

C₁-C₇ alkylene substituted with 0-6 R⁴, R⁸ or R¹⁵;

C₂-C₇ alkenylene substituted with 0-4 R⁴, R⁸ or R¹⁵;

C₂-C₇ alkynylene substituted with 0-4 R⁴, R⁸ or R¹⁵;

30

Y is selected from:

hydroxy,

C₁ to C₁₀ alkyloxy,

C₃ to C₁₁ cycloalkyloxy,

C₆ to C₁₀ aryloxy,

35

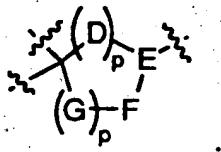
C₇ to C₁₁ aralkyloxy,

-55-

C₃ to C₁₀ alkylcarbonyloxyalkyloxy,
 C₃ to C₁₀ alkoxy carbonyloxyalkyloxy,
C₂ to C₁₀ alkoxy carbonylalkyloxy,
 C₅ to C₁₀ cycloalkylcarbonyloxyalkyloxy,
 5 C₅ to C₁₀ cycloalkoxycarbonyloxyalkyloxy,
 C₅ to C₁₀ cycloalkoxycarbonylalkyloxy,
 C₇ to C₁₁ aryloxycarbonylalkyloxy,
 C₈ to C₁₂ aryloxycarbonyloxyalkyloxy,
 C₈ to C₁₂ arylcarbonyloxyalkyloxy,
 10 C₅ to C₁₀ alkoxyalkylcarbonyloxyalkyloxy,
 C₅ to C₁₀ (5-alkyl-1,3-dioxa-cyclopenten-2-one-
 yl)methoxy,
 C₁₀ to C₁₄ (5-aryl-1,3-dioxa-cyclopenten-2-one-
 yl)methoxy;
 15 (R²) (R³) N-(C₁-C₁₀ alkoxy)-;

R¹⁴ and W are attached to the same carbon and taken
 together to form a spiro-fused, 5-7 membered ring
 structure of the formula:

20



D, E, F and G are each independently selected from:
 C(R^{6a})₂;
 25 carbonyl;
 a heteroatom moiety selected from N, N(R¹²), O,
 provided that no more than 2 of D, E, F and G
 are N, N(R¹²), O, S, or C(=O);
 alternatively, the bond between D and E, E and F, or F
 30 and G in such spiro-fused ring may be a
 carbon-nitrogen double bond or a carbon-carbon
 double bond;

-56-

R⁴ is selected from H, C₁-C₁₀ alkyl, hydroxy, C₁-C₁₀ alkoxy, nitro, C₁-C₁₀ alkylcarbonyl, or -N(R¹²)R¹³;

R⁶ and R⁷ are each independently selected from H, C₁-C₁₀ alkyl, hydroxy, C₁-C₁₀ alkoxy, nitro, C₁-C₁₀ alkylcarbonyl, -N(R¹²)R¹³, cyano, halo, CF₃, CHO, CO₂R^{5a}, C(=O)R^{5a}, CONHR^{5a}, CON(R¹²)₂, OC(=O)R^{5a}, OC(=O)OR^{5a}, OR^{5a}, OC(=O)N(R¹²)₂, OCH₂CO₂R^{5a}, CO₂CH₂CO₂R^{5a}, N(R¹²)₂, NO₂, NR¹²C(=O)R^{5a}, NR¹²C(=O)OR^{5a}, NR¹²C(=O)N(R¹²)₂, NR¹²SO₂N(R¹²)₂, NR¹²SO₂R^{5a}, S(O)_pR^{5a}, SO₂N(R¹²)₂, C₂ to C₆ alkenyl, C₃ to C₁₁ cycloalkyl, C₄ to C₁₁ cycloalkylmethyl;

C₆ to C₁₀ aryl optionally substituted with 1-3 groups selected from halogen, C₁-C₆ alkoxy, C₁-C₆ alkyl, CF₃, S(O)_mMe, or -NMe₂;

C₇ to C₁₁ arylalkyl, said aryl being optionally substituted with 1-3 groups selected from halogen, C₁-C₆ alkoxy, C₁-C₆ alkyl, CF₃, S(O)_mMe, or -NMe₂;

methylenedioxy when R⁶ is a substituent on aryl;

R^{6a} is selected from C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, CF₃, NO₂, or NR¹²R¹³;

R⁸ is selected from:

H;
R⁶;
C₁-C₁₀ alkyl, substituted with 0-8 R⁶;
C₂-C₁₀ alkenyl, substituted with 0-6 R⁶;
C₂-C₁₀ alkynyl, substituted with 0-6 R⁶;
C₃-C₈ cycloalkyl, substituted with 0-6 R⁶;
C₅-C₆ cycloalkenyl, substituted with 0-5 R⁶;
aryl, substituted with 0-5 R⁶;

-57-

5-6 membered heterocyclic ring containing 1-2 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-5 R⁶;

5

R¹² and R¹³ are independently H, C₁-C₁₀ alkyl, C₁-C₁₀ alkoxy carbonyl, C₁-C₁₀ alkyl carbonyl, C₁-C₁₀ alkylsulfonyl, aryl(C₁-C₁₀ alkyl)sulfonyl, 10 arylsulfonyl, aryl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, C₇-C₁₁ arylalkyl, C₂-C₇ alkyl carbonyl, C₇-C₁₁ aryl carbonyl, C₂-C₁₀ alkoxy carbonyl, C₄-C₁₁ cycloalkoxy carbonyl, C₇-C₁₁ bicycloalkoxy carbonyl, C₇-C₁₁ aryloxycarbonyl, 15 heteroaryl carbonyl, heteroarylalkyl carbonyl or aryl(C₁-C₁₀ alkoxy) carbonyl, wherein said aryls or heteroaryls are optionally substituted with 0-3 substituents selected from the group consisting of: C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, CF₃, and NO₂;

20

R⁵ and R^{5a} are selected independently from H, C₁ to C₈ alkyl, C₂ to C₆ alkenyl, C₃ to C₁₁ cycloalkyl, C₄ to C₁₁ cycloalkylmethyl, C₆ to C₁₀ aryl, C₇ to C₁₁ arylalkyl, or C₁-C₁₀ alkyl substituted with 0-8 R⁴;

25

R¹⁵ is selected from:

H;

R⁶;

C₁-C₁₀ alkyl, substituted with 0-8 R⁶;

30

C₂-C₁₀ alkenyl, substituted with 0-6 R⁶;

C₁-C₁₀ alkoxy, substituted with 0-6 R⁶;

aryl, substituted with 0-5 R⁶;

35

5-6 membered heterocyclic ring containing 1-2 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or

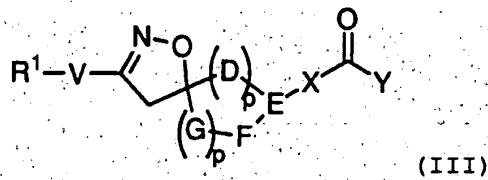
-58-

fully unsaturated, said heterocyclic ring
being substituted with 0-5 R⁶;
C₁-C₁₀ alkoxy carbonyl substituted with 0-8 R⁶;
CO₂R⁵; or
5 -C(=O)N(R¹²)R¹³;

n is 0-4;
p is 1-3;
q is 1-7;
10 r is 0-3;

provided that n, p, q and r are chosen such that the
number of atoms between R¹ and Y is in the range of
8-17.

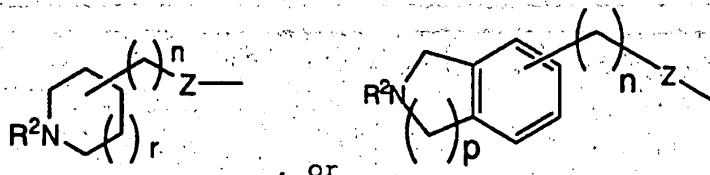
15 [17] Preferred compounds of this third embodiment
are compounds of Formula III:



20 wherein:

R¹ is selected from R²HN-, H₂N(R²N=)C-, H₂N(R²N=)CNH-,
R²HN(CH₂)_qO-, H₂N(R²N=)CNH(CH₂)_qO-,
piperazinyl-(CH₂)_qO-,

25



R² is selected from H, aryl(C₁-C₁₀ alkoxy)carbonyl, or
C₁-C₁₀ alkoxy carbonyl;

-59-

R⁴ is selected from H, C₁-C₁₀ alkyl, hydroxy, C₁-C₁₀ alkoxy, nitro, C₁-C₁₀ alkylcarbonyl, or -N(R¹²)R¹³;

V is selected from:
5 a single bond (i.e., V is absent);
C₁-C₇ alkylene substituted with 0-6 R⁶ or R⁷;
C₂-C₇ alkenylene substituted with 0-4 R⁶ or R⁷;
C₂-C₇ alkynylene substituted with 0-4 R⁶ or R⁷;
phenylene substituted with 0-3 R⁶ or R⁷;
10 pyridylene substituted with 0-3 R⁶ or R⁷;
pyridazinylene substituted with 0-3 R⁶ or R⁷;

X is selected from -(CH₂)_nC(=O)N(R¹²)-, C₁-C₇ alkylene substituted with 0-1 R⁴, C₂-C₇ alkenylene, or C₂-C₇ alkynylene;

Y is selected from:
hydroxy,
C₁ to C₁₀ alkyloxy,
20 C₃ to C₁₁ cycloalkyloxy,
C₆ to C₁₀ aryloxy,
C₇ to C₁₁ aralkyloxy,
C₃ to C₁₀ alkylcarbonyloxyalkyloxy,
C₃ to C₁₀ alkoxy carbonyloxyalkyloxy,
25 C₂ to C₁₀ alkoxy carbonylalkyloxy,
C₅ to C₁₀ cycloalkylcarbonyloxyalkyloxy,
C₅ to C₁₀ cycloalkoxycarbonyloxyalkyloxy,
C₅ to C₁₀ cycloalkoxycarbonylalkyloxy,
C₇ to C₁₁ aryloxycarbonylalkyloxy,
30 C₈ to C₁₂ aryloxycarbonyloxyalkyloxy,
C₈ to C₁₂ arylcarbonyloxyalkyloxy,
C₅ to C₁₀ alkoxyalkylcarbonyloxyalkyloxy,
C₅ to C₁₀ (5-alkyl-1,3-dioxa-cyclopenten-2-one-
y1)methyloxy, or

-60-

C₁₀ to C₁₄ (5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methoxy;

2 is selected from O or CH₂;

5

D, E, F and G are each independently selected from:

CH₂;

carbonyl;

a heteroatom moiety selected from N, NH, O, provided

10 that no more than 2 of D, E, F and G are N, NH, O or S;

alternatively, the bond between D and E, E and F, or F

and G in such spiro-fused ring may be a carbon-nitrogen double bond or a carbon-carbon

15 double bond;

R⁶ and R⁷ are each independently selected from H, C₁-C₁₀ alkyl, hydroxy, C₁-C₁₀ alkoxy, nitro, C₁-C₁₀ alkylcarbonyl, -N(R¹²)R¹³, cyano, or halo;

20

R¹² and R¹³ are each independently selected from H, C₁-C₁₀ alkyl, C₁-C₁₀ alkoxy carbonyl, C₁-C₁₀ alkylcarbonyl, C₁-C₁₀ alkylsulfonyl, aryl(C₁-C₁₀ alkyl)sulfonyl, arylsulfonyl, heteroarylcarbonyl, heteroaryalkylcarbonyl or aryl;

n is 0-4;

p is 1-3;

q is 1-7;

30 r is 0-3;

provided that n, p, q and r are chosen such that the number of atoms between R¹ and Y is in the range of 8-17.

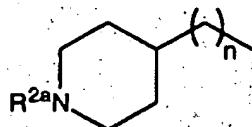
-61-

[18] Further preferred compounds of this third embodiment are compounds of Formula II wherein:

R¹ is R²NHC(=NR²)- and V is phenyl or pyridyl or

5

R¹ is



and V is a single bond (i.e. V

is absent);

10 n is 1 or 2;

X is C₁-C₄ alkylene substituted with 0-1 R⁴;

15 Y is selected from:

hydroxy;

C₁ to C₁₀ alkoxy;

methylcarbonyloxymethoxy-;

ethylcarbonyloxymethoxy-;

20 t-butylcarbonyloxymethoxy-;

cyclohexylcarbonyloxymethoxy-;

1-(methylcarbonyloxy)ethoxy-;

1-(ethylcarbonyloxy)ethoxy-;

1-(t-butylcarbonyloxy)ethoxy-;

25 1-(cyclohexylcarbonyloxy)ethoxy-;

i-propyloxycarbonyloxymethoxy-;

t-butyloxycarbonyloxymethoxy-;

1-(i-propyloxycarbonyloxy)ethoxy-;

1-(cyclohexyloxycarbonyloxy)ethoxy-;

30 1-(t-butyloxycarbonyloxy)ethoxy-;

dimethylaminoethoxy-;

diethylaminoethoxy-;

(5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;

-62-

(5-(*t*-butyl)-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;
(1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methoxy-;
1-(2-(2-methoxypropyl)carbonyloxy)ethoxy-;

5

R^{12} and R^{13} are each independently selected from H, C₁-C₆ alkyl, C₁-C₄ alkoxy carbonyl, C₁-C₄ alkyl carbonyl, C₁-C₄ alkylsulfonyl, aryl(C₁-C₄ alkyl)sulfonyl, arylsulfonyl, heteroaryl carbonyl, heteroaryl alkyl carbonyl or aryl; and

10

R^{13} is H.

15 [19] Specifically preferred compounds of this third embodiment are compounds, or pharmaceutically acceptable salt or prodrug forms thereof, selected from:

20 5(*R,S*)-3-(4-amidinophenyl)-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]non-2-ene-7,9-dione;
5(*R,S*)-3-(4-amidinophenyl)-8-(3-carboxypropyl)-1-oxa-2,8-diazaspiro[4.4]non-2-ene-7,9-dione;
5(*R,S*)-3-(4-amidinophenyl)-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]non-2-ene-5-one;
25 5(*R,S*)-3-(4-amidinophenyl)-8-(3-carboxypropyl)-1-oxa-2,8-diazaspiro[4.4]non-2-ene-5-one;
5(*R,S*)-3-(4-amidinophenyl)-8-(2-carboxyethyl)-1-oxa-2-azaspiro[4.4]nona-2,8-diene-5-one;
5(*R,S*)-3-(4-amidinophenyl)-8-(3-carboxypropyl)-1-oxa-2-azaspiro[4.4]nona-2,8-diene-5-one;
30 5(*R,S*)-3-(4-amidinophenyl)-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]dec-2-ene-7,9-dione;
5(*R,S*)-3-(4-amidinophenyl)-8-(3-carboxypropyl)-1-oxa-2,8-diazaspiro[4.4]dec-2-ene-7,9-dione;
35 5(*R,S*)-3-(4-amidinophenyl)-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]dec-2-ene-5-one;

-63-

5 (R, S)-3-(4-amidinophenyl)-8-(3-carboxypropyl)-1-oxa-2,8-diazaspiro[4.4]dec-2-ene-5-one;

5 (R, S)-3-(4-amidinophenyl)-8-(2-carboxyethyl)-1-oxa-2-azaspiro[4.4]deca-2,8-diene-5-one;

5 5 (R, S)-3-(4-amidinophenyl)-8-(3-carboxypropyl)-1-oxa-2-azaspiro[4.4]deca-2,8-diene-5-one;

5 (R, S)-3-(4-amidinophenyl)-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]undec-2-ene-7,9-dione;

10 5 (R, S)-3-(4-amidinophenyl)-8-(3-carboxypropyl)-1-oxa-2,8-diazaspiro[4.4]undec-2-ene-7,9-dione;

5 (R, S)-3-(4-amidinophenyl)-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]undec-2-ene-5-one;

5 (R, S)-3-(4-amidinophenyl)-8-(3-carboxypropyl)-1-oxa-2,8-diazaspiro[4.4]undec-2-ene-5-one;

15 5 (R, S)-3-(4-amidinophenyl)-8-(2-carboxyethyl)-1-oxa-2-azaspiro[4.4]undeca-2,8-diene-5-one;

5 (R, S)-3-(4-amidinophenyl)-8-(3-carboxypropyl)-1-oxa-2-azaspiro[4.4]undeca-2,8-diene-5-one;

20 5 (R, S)-3-[2-(piperidin-4-yl)ethyl]-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]non-2-ene-7,9-dione;

5 (R, S)-3-[2-(piperidin-4-yl)ethyl]-8-(3-carboxypropyl)-1-oxa-2,8-diazaspiro[4.4]non-2-ene-7,9-dione;

25 5 (R, S)-3-[2-(piperidin-4-yl)ethyl]-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]non-2-ene-5-one;

5 (R, S)-3-[2-(piperidin-4-yl)ethyl]-8-(2-carboxyethyl)-1-oxa-2-azaspiro[4.4]nona-2,8-diene-5-one;

30 5 (R, S)-3-[2-(piperidin-4-yl)ethyl]-8-(3-carboxypropyl)-1-oxa-2-azaspiro[4.4]nona-2,8-diene-5-one;

5 (R, S)-3-[2-(piperidin-4-yl)ethyl]-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]dec-2-ene-7,9-dione;

35 5 (R, S)-3-[2-(piperidin-4-yl)ethyl]-8-(3-carboxypropyl)-1-oxa-2,8-diazaspiro[4.4]dec-2-ene-5,7-dione;

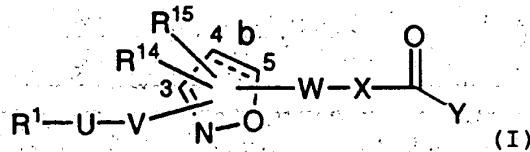
5 (R, S)-3-[2-(piperidin-4-yl)ethyl]-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]dec-2-ene-5-one;

-64-

5 (R,S)-3-[2-(piperidin-4-yl)ethyl]-8-(3-carboxypropyl)-
1-oxa-2,8-diazaspiro[4.4]dec-2-ene-5-one;
5 (R,S)-3-[2-(piperidin-4-yl)ethyl]-8-(2-carboxyethyl)-1-
oxa-2-azaspiro[4.4]deca-2,8-diene-5-one;
5 5 (R,S)-3-[2-(piperidin-4-yl)ethyl]-8-(3-carboxypropyl)-
1-oxa-2-azaspiro[4.4]deca-2,8-diene-5-one;
5 (R,S)-3-[2-(piperidin-4-yl)ethyl]-8-(2-carboxyethyl)-1-
oxa-2,8-diazaspiro[4.4]undec-2-ene-7,9-dione;
5 (R,S)-3-[2-(piperidin-4-yl)ethyl]-8-(3-carboxypropyl)-
1-oxa-2,8-diazaspiro[4.4]undec-2-ene-7,9-dione;
5 (R,S)-3-[2-(piperidin-4-yl)ethyl]-8-(2-carboxyethyl)-1-
oxa-2,8-diazaspiro[4.4]undec-2-ene-5-one;
5 (R,S)-3-[2-(piperidin-4-yl)ethyl]-8-(3-carboxypropyl)-
1-oxa-2,8-diazaspiro[4.4]undec-2-ene-5-one;
15 5 (R,S)-3-[2-(piperidin-4-yl)ethyl]-8-(2-carboxyethyl)-1-
oxa-2-azaspiro[4.4]undeca-2,8-diene-5-one;
5 (R,S)-3-[2-(piperidin-4-yl)ethyl]-8-(3-carboxypropyl)-
1-oxa-2-azaspiro[4.4]undeca-2,8-diene-5-one;
5 (R,S)-3-(4-amidinophenyl)-8-
20 [2-(benzyloxycarbonylamino)-2-carboxyethyl]-1-oxa-
2,8-diazaspiro[4.5]dec-2-ene.

[20] A fourth embodiment of this invention provides
compounds of Formula I:

25



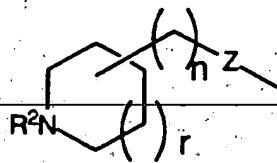
or pharmaceutically acceptable salt or prodrug forms
thereof, wherein:

30

R¹ is selected from:

R²(R³)N(CH₂)_qZ⁻, R²(R³)N(R²N=)C(CH₂)_qZ⁻,

R²(R³)N(R²N=)CN(R²)(CH₂)_qZ⁻, piperazinyl-(CH₂)_qZ⁻ or



Z is selected from O, S, S(=O), S(=O)2;

5 R² and R³ are independently selected from: H, C₁-C₁₀ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, C₆-C₁₀ aryl, C₇-C₁₁ arylalkyl, C₂-C₇ alkylcarbonyl, C₇-C₁₁ arylcarbonyl, C₂-C₁₀ alkoxy carbonyl, C₄-C₁₁ cycloalkoxy carbonyl, C₇-C₁₁ bicycloalkoxy carbonyl, C₇-C₁₁ aryloxy carbonyl, or 10 aryl(C₁-C₁₀ alkoxy) carbonyl, C₁-C₆ alkylcarbonyloxy(C₁-C₄ alkoxy) carbonyl, C₆-C₁₀ arylcarbonyloxy(C₁-C₄ alkoxy) carbonyl, C₄-C₁₁ cycloalkylcarbonyloxy(C₁-C₄ alkoxy) carbonyl;

15

U is optionally present and is selected from C₁-C₇ alkylene, C₂-C₇ alkenylene, C₂-C₇ alkynylene, arylene, or pyridylene;

V is selected from:

20

a single bond (i.e., V is absent); C₁-C₇ alkylene substituted with 0-6 R⁶ or R⁷; C₂-C₇ alkenylene substituted with 0-4 R⁶ or R⁷; C₂-C₇ alkynylene substituted with 0-4 R⁶ or R⁷; phenylene substituted with 0-4 R⁶ or R⁷; 25 pyridylene substituted with 0-3 R⁶ or R⁷; pyridazinylene substituted with 0-3 R⁶ or R⁷;

W is -(aryl)-Z¹-, wherein said aryl is substituted with 0-6 R⁶ or R⁷;

30

Z¹ is selected from a single bond (i.e., Z¹ is absent), -CH₂-, O or S;

X is selected from:

a single bond (i.e., X is absent);

C₁-C₇ alkylene substituted with 0-6 R⁴, R⁸ or R¹⁵;

5 C₂-C₇ alkenylene substituted with 0-4 R⁴, R⁸ or R¹⁵;

C₂-C₇ alkynylene substituted with 0-4 R⁴, R⁸ or R¹⁵;

Y is selected from hydroxy, C₁ to C₁₀ alkyloxy, C₃ to

C₁₁ cycloalkyloxy, C₆ to C₁₀ aryloxy, C₇ to C₁₁

10 aralkyloxy, C₃ to C₁₀ alkylcarbonyloxyalkyloxy, C₃

to C₁₀ alkoxy carbonyloxyalkyloxy, C₂ to C₁₀

alkoxycarbonylalkyloxy, C₅ to C₁₀

cycloalkylcarbonyloxyalkyloxy, C₅ to C₁₀

cycloalkoxycarbonyloxyalkyloxy, C₅ to C₁₀

15 cycloalkoxycarbonylalkyloxy, C₇ to C₁₁

aryloxycarbonylalkyloxy, C₈ to C₁₂

aryloxycarbonyloxyalkyloxy, C₈ to C₁₂

arylcarbonyloxyalkyloxy, C₅ to C₁₀

alkoxyalkylcarbonyloxyalkyloxy, C₅ to C₁₀ (5-alkyl-

20 1,3-dioxa-cyclopenten-2-one-yl)methyloxy, C₁₀ to C₁₄

(5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy;

(R²) (R³) N-(C₁-C₁₀ alkoxy)-;

R⁴ is selected from H, C₁-C₁₀ alkyl, hydroxy, C₁-C₁₀

25 alkoxy, nitro, C₁-C₁₀ alkylcarbonyl, or -N(R¹²)R¹³;

R⁶ and R⁷ are each independently selected from H, C₁-C₁₀

alkyl, hydroxy, C₁-C₁₀ alkoxy, nitro, C₁-C₁₀

alkylcarbonyl, -N(R¹²)R¹³, cyano, halo, CF₃, CHO,

30 CO₂R^{5a}, C(=O)R^{5a}, CONHR^{5a}, CON(R¹²)₂, OC(=O)R^{5a},

OC(=O)OR^{5a}, OR^{5a}, OC(=O)N(R¹²)₂, OCH₂CO₂R^{5a},

CO₂CH₂CO₂R^{5a}, N(R¹²)₂, NO₂, NR¹²C(=O)R^{5a},

NR¹²C(=O)OR^{5a}, NR¹²C(=O)N(R¹²)₂, NR¹²SO₂N(R¹²)₂,

NR¹²SO₂R^{5a}, S(O)pR^{5a}, SO₂N(R¹²)₂, C₂ to C₆ alkenyl,

35 C₃ to C₁₁ cycloalkyl, C₄ to C₁₁ cycloalkylmethyl;

-67-

C₆ to C₁₀ aryl optionally substituted with halogen, alkoxy, alkyl, -CF₃, S(O)_mMe, or -NMe₂; or

5 C₇ to C₁₁ arylalkyl said aryl being optionally substituted with halogen, alkoxy, alkyl, -CF₃, S(O)_mMe, or -NMe₂;

R⁸ is selected from:

H;

10 R⁶;
C₁-C₁₀ alkyl, substituted with 0-8 R⁶;
C₂-C₁₀ alkenyl, substituted with 0-6 R⁶;
C₂-C₁₀ alkynyl, substituted with 0-6 R⁶;
C₃-C₈ cycloalkyl, substituted with 0-6 R⁶;
15 C₅-C₆ cycloalkenyl, substituted with 0-5 R⁶;
aryl, substituted with 0-5 R⁶;
5-6 membered heterocyclic ring containing 1-2 N, O,
or S heteroatoms, wherein said heterocyclic
ring may be saturated, partially saturated, or
20 fully unsaturated, said heterocyclic ring
being substituted with 0-5 R⁶;

R¹² and R¹³ are independently H, C₁-C₁₀ alkyl, C₁-C₁₀ alkoxy carbonyl, C₁-C₁₀ alkyl carbonyl, C₁-C₁₀ alkylsulfonyl, aryl(C₁-C₁₀ alkyl)sulfonyl,
25 arylsulfonyl, aryl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, C₇-C₁₁ arylalkyl,
C₂-C₇ alkyl carbonyl, C₇-C₁₁ aryl carbonyl, C₂-C₁₀ alkoxy carbonyl, C₄-C₁₁ cycloalkoxy carbonyl, C₇-C₁₁
30 bicycloalkoxy carbonyl, C₇-C₁₁ aryloxy carbonyl, heteroaryl carbonyl, heteroarylalkyl carbonyl or
aryl(C₁-C₁₀ alkoxy) carbonyl;

-68-

R^{14} is selected from H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, aryl, heteroaryl or C₁-C₁₀ alkoxy carbonyl, CO₂R⁵ or -C(=O)N(R¹²)R¹³;

5 R⁵ and R^{5a} are selected independently from H, C₁ to C₈ alkyl, C₂ to C₆ alkenyl, C₃ to C₁₁ cycloalkyl, C₄ to C₁₁ cycloalkylmethyl, C₆ to C₁₀ aryl, C₇ to C₁₁ arylalkyl, or C₁-C₁₀ alkyl substituted with 0-8 R⁴;

10 R¹⁵ is selected from:

H;

R⁶;

C₁-C₁₀ alkyl, substituted with 0-8 R⁶;

C₂-C₁₀ alkenyl, substituted with 0-6 R⁶;

15 C₁-C₁₀ alkoxy, substituted with 0-6 R⁶;

aryl, substituted with 0-5 R⁶;

5-6 membered heterocyclic ring containing 1-2 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-5 R⁶;

20 C₁-C₁₀ alkoxy carbonyl substituted with 0-8 R⁶;

CO₂R⁵; or

-C(=O)N(R¹²)R¹³;

25

n is 0-4;

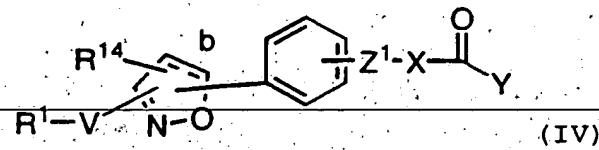
q is 2-7;

r is 0-3;

provided that n, q, and r are chosen such that the

30 number of atoms between R¹ and Y is about 8-17.

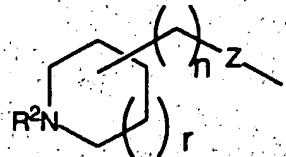
[21] Preferred compounds of this fourth embodiment are those of Formula IV:



wherein:

10 R^1 is selected from $R^2HN(CH_2)_qO^-$,

15 $R^2HN(R^2N=C)NH(CH_2)_qO^-$, piperazinyl- $(CH_2)_qO^-$, or



20 Z is O ;

25 R^2 is selected from H, aryl(C_1-C_{10})alkoxycarbonyl,
 C_1-C_{10} alkoxycarbonyl;

30 V is selected from:

a single bond (i.e., V is absent);

35 C_1-C_7 alkylene substituted with 0-6 R^6 or R^7 ;

C_2-C_7 alkenylene substituted with 0-4 R^6 or R^7 ;

C_2-C_7 alkynylene substituted with 0-4 R^6 or R^7 ;

phenylene substituted with 0-3 R^6 or R^7 ;

pyridylene substituted with 0-3 R^6 or R^7 ;

40 pyridazinylene substituted with 0-3 R^6 or R^7 ;

45 Z^1 is selected from a single bond (i.e., Z^1 is absent),
 O or S ;

50 X is selected from:

a single bond (i.e., X is absent);

C_1-C_7 alkylene substituted with 0-4 R^4 , R^8 or R^{15} ;

C_2-C_7 alkenylene substituted with 0-3 R^4 , R^8 or R^{15} ;

C_2-C_7 alkynylene substituted with 0-3 R^4 , R^8 or R^{15} ;

55

-70-

Y selected from hydroxy, C₁ to C₁₀ alkyloxy, C₃ to C₁₁ cycloalkyloxy, C₆ to C₁₀ aryloxy, C₇ to C₁₁ aralkyloxy, C₃ to C₁₀ alkylcarbonyloxyalkyloxy, C₃ to C₁₀ alkoxy carbonyloxyalkyloxy, C₂ to C₁₀ alkoxy carbonylalkyloxy, C₅ to C₁₀ cycloalkylcarbonyloxyalkyloxy, C₅ to C₁₀ cycloalkoxycarbonyloxyalkyloxy, C₅ to C₁₀ cycloalkoxycarbonylalkyloxy, C₇ to C₁₁ aryloxycarbonylalkyloxy, C₈ to C₁₂ aryloxycarbonyloxyalkyloxy, C₈ to C₁₂ arylcarbonyloxyalkyloxy, C₅ to C₁₀ alkoxyalkylcarbonyloxyalkyloxy, C₅ to C₁₀ (5-alkyl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy, or C₁₀ to C₁₄ (5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy;

R⁴ is selected from H, C₁-C₁₀ alkyl, hydroxy, C₁-C₁₀ alkoxy, nitro, C₁-C₁₀ alkylcarbonyl, or -N(R¹²)R¹³;

20 R⁶ and R⁷ are selected from H, C₁-C₁₀ alkyl, hydroxy, C₁-C₁₀ alkoxy, nitro, C₁-C₁₀ alkylcarbonyl, -N(R¹²)R¹³, cyano, or halo;

25 R⁸ is selected from H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₃-C₈ cycloalkyl, C₅-C₆ cycloalkenyl, aryl, 5-6 membered heterocyclic ring containing 1-2 N, O, or S, where said heterocyclic ring may be saturated, partially saturated, or fully unsaturated;

30 R¹² and R¹³ are independently selected from H, C₁-C₁₀ alkyl, C₁-C₁₀ alkoxy carbonyl, C₁-C₁₀ alkylcarbonyl, C₁-C₁₀ alkylsulfonyl, aryl(C₁-C₁₀ alkyl)sulfonyl, arylsulfonyl, heteroarylcarbonyl, heteroarylalkylcarbonyl or aryl;

-71-

14 R¹⁴ is selected from H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, aryl, heteroaryl or C₁-C₁₀ alkoxy carbonyl, CO₂R⁵ or -C(=O)N(R¹²)R¹³;

5 R⁵ is selected from H or C₁-C₁₀ alkyl substituted with 0-6 R⁴;

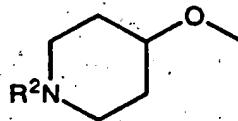
n is 0-4;

q is 2-7;

10 provided that n and q are chosen such that the number of atoms between R¹ and Y is in the range of 8-17.

[22] Further preferred compounds of this fourth embodiment are compounds of Formula IV wherein:

15 R¹ is R²HN(CH₂)_qO- or



20 V is C₁-C₃ alkylene;

Z¹ is a single bond (i.e. Z¹ is absent) or O;

X is C₁-C₃ alkylene substituted with 0-1 R⁴;

25 Y is selected from:

hydroxy;

C₁ to C₁₀ alkoxy;

methylcarbonyloxymethoxy-;

30 ethylcarbonyloxymethoxy-;

t-butylcarbonyloxymethoxy-;

cyclohexylcarbonyloxymethoxy-;

1-(methylcarbonyloxy)ethoxy-;

1-(ethylcarbonyloxy)ethoxy-;

-72-

1-(*t*-butyloxycarbonyloxy)ethoxy-;
1-(cyclohexyloxycarbonyloxy)ethoxy-;
i-propyloxycarbonyloxymethoxy-;
t-butyloxycarbonyloxymethoxy-;
5 1-(*i*-propyloxycarbonyloxy)ethoxy-;
1-(cyclohexyloxycarbonyloxy)ethoxy-;
1-(*t*-butyloxycarbonyloxy)ethoxy-;
dimethylaminoethoxy-;
diethylaminoethoxy-;
10 (5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;
(5-(*t*-butyl)-1,3-dioxacyclopenten-2-on-4-
yl)methoxy-;
(1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methoxy-;
1-(2-(2-methoxypropyl)carbonyloxy)ethoxy-;

15 *R*¹² and *R*¹³ are independently selected from H, C₁-C₆
alkyl, C₁-C₄ alkoxy carbonyl, C₁-C₄ alkyl carbonyl,
C₁-C₆ alkylsulfonyl, aryl(C₁-C₄ alkyl)sulfonyl,
arylsulfonyl, heteroaryl carbonyl,
20 heteroaryl alkyl carbonyl or aryl;

*R*¹³ is H.

[23] Specifically preferred compounds of this fourth
25 embodiment are compounds, or pharmaceutically acceptable
salt or prodrug forms thereof, selected from:

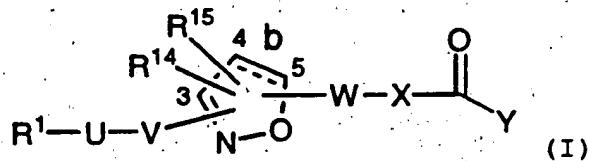
5 (R, S)-4-[3-(piperidin-4-yl)oxymethylisoxazolin-5-yl]hy-
drocinnamic acid;
30 5 (R, S)-4-[3-(2-aminoethoxymethyl)isoxazolin-5-yl]hydro-
cinnamic acid;
5 (R, S)-4-[3-(3-aminopropoxymethyl)isoxazolin-5-yl]hy-
drocinnamic acid;
35 5 (R, S)-4-[3-(piperidin-4-yl)oxymethylisoxazolin-5-
yl]phenoxyacetic acid;

5 (R, S)-4-[3-(2-aminoethoxymethyl)isoxazolin-5-yl]phenoxycetic acid;

5 (R, S)-4-[3-(3-aminopropoxyloxymethyl)isoxazolin-5-yl]phenoxyacetic acid.

5

[24] A fifth embodiment of this invention provides a compound of Formula I:

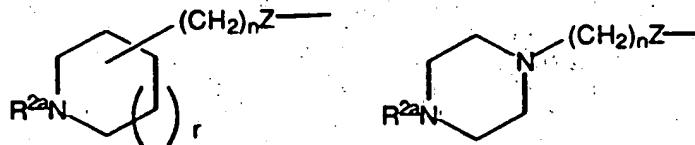


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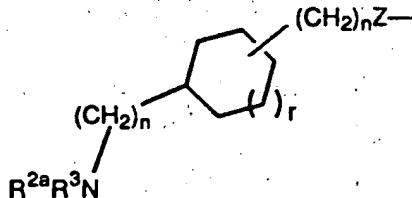
or a pharmaceutically acceptable salt or prodrug form thereof, wherein:

b is a single or double bond;

15 R¹ is selected from R^{2a}(R³)N-, R²(R³)N(R²N=)C-, R^{2a}(R³)N(CH₂)_qZ-, R²(R³)N(R²N=)C(CH₂)_qZ-,



or



20

Z is selected from a bond (i.e. is absent), O, S, S(=O), S(=O)₂;

25 R² and R³ are independently selected from: H, C₁-C₁₀ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, C₆-C₁₀ aryl, C₇-C₁₁ arylalkyl, C₂-C₇

alkylcarbonyl, C₇-C₁₁ arylcarbonyl, C₂-C₁₀
alkoxycarbonyl, C₄-C₁₁ cycloalkoxycarbonyl, C₇-C₁₁
bicycloalkoxycarbonyl, C₇-C₁₁ aryloxycarbonyl,
aryl(C₁-C₁₀ alkoxy)carbonyl,
5 alkylcarbonyloxyalkoxycarbonyl, or
alkoxycarbonyloxyalkoxycarbonyl, C₁-C₆
alkylcarbonyloxy(C₁-C₄ alkoxy)carbonyl, C₆-C₁₀
arylcarbonyloxy(C₁-C₄ alkoxy)carbonyl, C₄-C₁₁
cycloalkylcarbonyloxy(C₁-C₄ alkoxy)carbonyl;

10

R^{2a} is R² or R²(R³)N(R²N=)C;

U is selected from:

a single bond (i.e., U is not present),
15 -(C₁-C₇ alkyl)-,
-(C₂-C₇ alkenyl)-,
-(C₂-C₇ alkynyl)-,
-(aryl)- substituted with 0-3 R^{6a}, or
-(pyridyl)- substituted with 0-3 R^{6a};

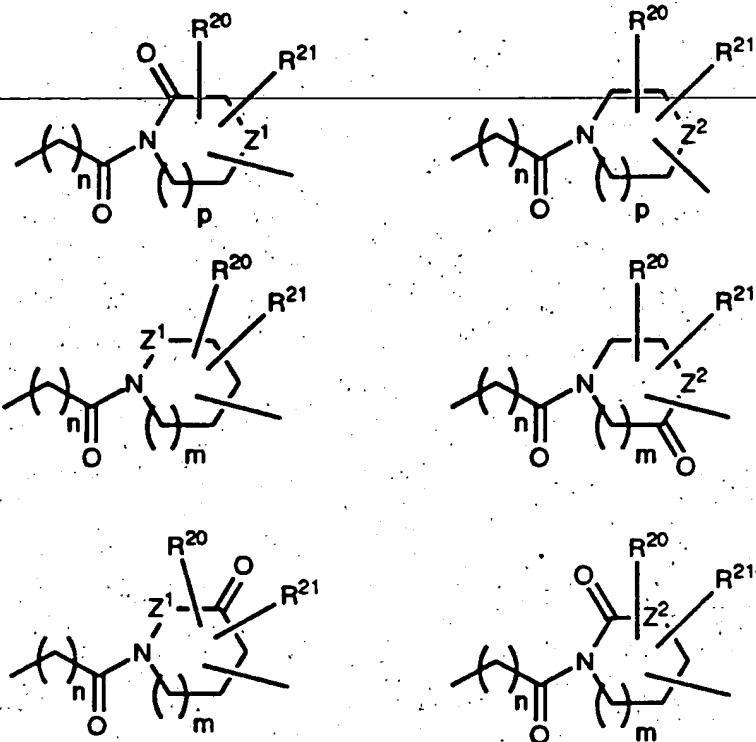
20

V is selected from:

a single bond (i.e., V is not present);
25 -(C₁-C₇ alkyl)-, substituted with 0-3 groups
independently selected from R⁶ or R⁷;
-(C₂-C₇ alkenyl)-, substituted with 0-3 groups
independently selected from R⁶ or R⁷;
-(C₂-C₇ alkynyl)-, substituted with 0-3 groups
independently selected from R⁶ or R⁷;
-(phenyl)-, substituted with 0-2 groups
independently selected from R⁶ or R⁷;
30 -(pyridyl)-, substituted with 0-2 groups
independently selected from R⁶ or R⁷; or
-(pyridazinyl)-, substituted with 0-2 groups
independently selected from R⁶ or R⁷;

35

W is selected from:



X is selected from:

5 a single bond (i.e. X is absent)
 $-(C(R^4)_2)_n-C(R^4)(R^8)-C(R^4)(R^{4a})-$, with the proviso
 that when n is 0 or 1, then at least one of R^{4a} or
 R^8 is other than H or methyl;

10 Y is selected from:

hydroxy,
 C_1 to C_{10} alkyloxy,
 C_3 to C_{11} cycloalkyloxy,
 C_6 to C_{10} aryloxy,
15 C_7 to C_{11} aralkyloxy,
 C_3 to C_{10} alkylcarbonyloxyalkyloxy,
 C_3 to C_{10} alkoxy carbonyloxyalkyloxy,
 C_2 to C_{10} alkoxy carbonylalkyloxy,
 C_5 to C_{10} cycloalkylcarbonyloxyalkyloxy,
20 C_5 to C_{10} cycloalkoxycarbonyloxyalkyloxy,

C₅ to C₁₀ cycloalkoxycarbonylalkyloxy,
C₇ to C₁₁ aryloxycarbonylalkyloxy,
C₈ to C₁₂ aryloxycarbonyloxyalkyloxy,
C₈ to C₁₂ arylcarbonyloxyalkyloxy,
5 C₅ to C₁₀ alkoxyalkylcarbonyloxyalkyloxy,
C₅ to C₁₀ (5-alkyl-1,3-dioxa-cyclopenten-2-one-
yl)methyloxy,
C₁₀ to C₁₄ (5-aryl-1,3-dioxa-cyclopenten-2-one-
yl)methyloxy,
10 (R²) (R³) N-(C₁-C₁₀ alkoxy)-;

Z¹ is -C-, -O-, or -NR²²-;

Z² is -O-, or -NR²²-;

15 R⁴ is selected from H, C₁-C₁₀ alkyl, C₁-C₁₀
alkylcarbonyl, aryl, arylalkylene cycloalkyl, or
cycloalkylalkylene;

20 alternately, two R⁴ groups on adjacent carbons may join
to form a bond (i.e. a carbon-carbon double or
triple bond);

25 R^{4a} is selected from H, hydroxy, C₁-C₁₀ alkoxy, nitro,
N(R⁵)R^{5a}, -N(R¹²)R¹³, -N(R¹⁶)R¹⁷,
C₁-C₁₀ alkyl substituted with 0-3 R⁶,
aryl substituted with 0-3 R⁶, or
C₁-C₁₀ alkylcarbonyl;

30 R^{4b} is selected from H, C₁-C₆ alkyl, C₂-C₆ alkenyl,
C₂-C₆ alkynyl, hydroxy, C₁-C₆ alkoxy, C₁-C₆
alkylthio, C₁-C₆ alkylsulfinyl, C₁-C₆ alkylsulfonyl,
nitro, C₁-C₆ alkylcarbonyl, C₆-C₁₀ aryl, -N(R¹²)R¹³,
halo, CF₃, CN, C₁-C₆ alkoxy carbonyl, carboxy,
35 piperidinyl, or pyridyl;

5 R^5 is selected from H, C₁-C₈ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylmethyl, C₆-C₁₀ aryl, C₇-C₁₁ arylalkyl, or C₁-C₁₀ alkyl substituted with 0-2 R^{4b};

10 R^{5a} is selected from hydrogen, hydroxy, C₁ to C₈ alkyl, C₂ to C₆ alkenyl, C₃ to C₁₁ cycloalkyl, C₄ to C₁₁ cycloalkylmethyl, C₁-C₆ alkoxy, benzyloxy, C₆ to C₁₀ aryl, heteroaryl, C₇ to C₁₁ arylalkyl, or C₁-C₁₀ alkyl substituted with 0-2 R^{4b};

15 alternately, R⁵ and R^{5a} when both are substituents on the same nitrogen atom (as in -NR⁵R^{5a}) can be taken together with the nitrogen atom to which they are attached to form 3-azabicyclononyl, 1,2,3,4-tetrahydro-1-quinolinyl, 1,2,3,4-tetrahydro-2-isoquinolinyl, 1-piperidinyl, 1-morpholinyl, 1-pyrrolidinyl, thiamorpholinyl, thiazolidinyl or 1-piperazinyl, each being optionally substituted with C₁-C₆ alkyl, C₆-C₁₀ aryl, heteroaryl, C₇-C₁₁ arylalkyl, C₁-C₆ alkylcarbonyl, C₃-C₇ cycloalkylcarbonyl, C₁-C₆ alkoxy carbonyl, C₇-C₁₁ arylalkoxycarbonyl, C₁-C₆ alkylsulfonyl or C₆-C₁₀ arylsulfonyl;

20 R^{5b} is selected from C₁-C₈ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylmethyl, C₆-C₁₀ aryl, C₇-C₁₁ arylalkyl, or C₁-C₁₀ alkyl substituted with 0-2 R^{4b};

25 R^6 is selected from H, C₁-C₁₀ alkyl, hydroxy, C₁-C₁₀ alkoxy, nitro, C₁-C₁₀ alkylcarbonyl, -N(R¹²)R¹³, cyano, halo, CF₃, CHO, CO₂R⁵, C(=O)R^{5a}, CONR⁵R^{5a}, OC(=O)R^{5a}, OC(=O)OR^{5b}, OR⁵, OC(=O)NR⁵R^{5a}, OCH₂CO₂R⁵, CO₂CH₂CO₂R⁵, NO₂, NR^{5a}C(=O)R^{5a}, NR^{5a}C(=O)OR^{5b},

NR^{5a}C(=O)NR^{5a}R^{5a}, NR^{5a}SO₂NR^{5a}R^{5a}, NR^{5a}SO₂R⁵, S(O)_pR⁵,
SO₂NR^{5a}, C₂ to C₆ alkenyl, C₃ to C₁₁ cycloalkyl,
C₄ to C₁₁ cycloalkylmethyl;

5 C₆ to C₁₀ aryl optionally substituted with 1-3
groups selected from halogen, C₁-C₆ alkoxy, C₁-C₆
alkyl, CF₃, S(O)_mMe, or -NMe₂;

10 C₇ to C₁₁ arylalkyl; said aryl being optionally
substituted with 1-3 groups selected from halogen,
C₁-C₆ alkoxy, C₁-C₆ alkyl, CF₃, S(O)_mMe, or -NMe₂;

methylenedioxy when R⁶ is a substituent on aryl; or

15 a 5-6 membered heterocyclic ring containing 1-2 N,
O, or S heteroatoms, wherein said heterocyclic
ring may be saturated, partially saturated, or
fully unsaturated, said heterocyclic ring
being substituted with 0-2 R⁷;

20 R^{6a} is selected from C₁-C₄ alkyl, C₁-C₄ alkoxy, halo,
CF₃, NO₂, or NR¹²R¹³;

25 R⁷ is selected from H, C₁-C₁₀ alkyl, hydroxy, C₁-C₁₀
alkoxy, nitro, C₁-C₁₀ alkylcarbonyl, -N(R¹²)R¹³,
cyano, halo, CF₃, CHO, CO₂R⁵, C(=O)R^{5a}, CONR^{5a}R^{5a},
OC(=O)R^{5a}, OC(=O)OR^{5b}, OR^{5a}, OC(=O)NR^{5a}R^{5a}, OCH₂CO₂R⁵,
CO₂CH₂CO₂R⁵, NO₂, NR^{5a}C(=O)R^{5a}, NR^{5a}C(=O)OR^{5b},
NR^{5a}C(=O)NR^{5a}, NR^{5a}SO₂NR^{5a}, NR^{5a}SO₂R⁵, S(O)_mR^{5a},
SO₂NR^{5a}, C₂ to C₆ alkenyl, C₃ to C₁₁ cycloalkyl,
C₄ to C₁₁ cycloalkylmethyl, C₆ to C₁₀ aryl, or C₇ to
C₁₁ arylalkyl;

30 R⁸ is selected from:
35 R⁶;

C₂-C₁₀ alkyl, substituted with 0-3 R⁶;
C₂-C₁₀ alkenyl, substituted with 0-3 R⁶;
C₂-C₁₀ alkynyl, substituted with 0-3 R⁶;

5 C₃-C₈ cycloalkyl, substituted with 0-3 R⁶;
C₅-C₆ cycloalkenyl, substituted with 0-3 R⁶;
aryl, substituted with 0-3 R⁶;
10 5-6 membered heterocyclic ring containing 1-2 N, O,
or S heteroatoms, wherein said heterocyclic
ring may be saturated, partially saturated, or
fully unsaturated, said heterocyclic ring
being substituted with 0-2 R⁶;

R¹² and R¹³ are independently H, C₁-C₁₀ alkyl, C₁-C₁₀
15 alkoxycarbonyl, C₁-C₁₀ alkylcarbonyl, C₁-C₁₀
alkylsulfonyl, aryl(C₁-C₁₀ alkyl)sulfonyl,
arylsulfonyl, aryl, C₂-C₆ alkenyl, C₃-C₁₁
cycloalkyl, C₄-C₁₁ cycloalkylalkyl, C₇-C₁₁ arylalkyl,
C₇-C₁₁ arylcarbonyl, C₄-C₁₁ cycloalkoxycarbonyl, C₇-
20 C₁₁ bicycloalkoxycarbonyl, C₇-C₁₁ aryloxycarbonyl,
or aryl(C₁-C₁₀ alkoxy)carbonyl, wherein said aryls
are optionally substituted with 0-3 substituents
selected from the group consisting of: C₁-C₄ alkyl,
C₁-C₄ alkoxy, halo, CF₃, and NO₂;

25 R¹⁴ is selected from H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl,
C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, aryl, heteroaryl or
C₁-C₁₀ alkoxycarbonyl, CO₂R⁵ or -C(=O)N(R⁵)R^{5a};

R¹⁵ is selected from:
30 H;
R⁶;
C₁-C₁₀ alkyl, substituted with 0-3 R⁶;
C₂-C₁₀ alkenyl, substituted with 0-3 R⁶;
C₁-C₁₀ alkoxy, substituted with 0-3 R⁶;
35 aryl, substituted with 0-3 R⁶;

5-6 membered heterocyclic ring containing 1-2 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-2 R⁶;

5 C₁-C₁₀ alkoxy carbonyl substituted with 0-2 R⁶;

-CO₂R⁵; or

-C(=O)N(R¹²)R¹³;

provided that when b is a double bond, only one of R¹⁴ 10 or R¹⁵ is present;

R¹⁶ is selected from:

-C(=O)-O-R^{18a},

-C(=O)-R^{18b},

15 -C(=O)N(R^{18b})₂,

-C(=O)NHSO₂R^{18a},

-C(=O)NHC(=O)R^{18b},

-C(=O)NHC(=O)OR^{18a},

-C(=O)NHSO₂NHR^{18b},

20 -C(=S)-NH-R^{18b},

-NH-C(=O)-O-R^{18a},

-NH-C(=O)-R^{18b},

-NH-C(=O)-NH-R^{18b},

-SO₂-O-R^{18a},

25 -SO₂-R^{18a},

-SO₂-N(18b)₂,

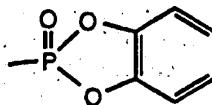
-SO₂-NHC(=O)O18b,

-P(=S)(OR^{18a})₂,

-P(=O)(OR^{18a})₂,

30 -P(=S)(R^{18a})₂,

-P(=O)(R^{18a})₂, or



R¹⁷ is selected from: H, C₁-C₁₀ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₅ cycloalkylalkyl, aryl, aryl(C₁-C₁₀ alkyl)-;

5 R^{18a} is selected from:

C₁-C₈ alkyl substituted with 0-2 R¹⁹,
C₂-C₈ alkenyl substituted with 0-2 R¹⁹,
C₂-C₈ alkynyl substituted with 0-2 R¹⁹,
C₃-C₈ cycloalkyl substituted with 0-2 R¹⁹,
10 aryl substituted with 0-4 R¹⁹,
aryl(C₁-C₆ alkyl)- substituted with 0-4 R¹⁹,

15 a 5-10 membered heterocyclic ring system having 1-3 heteroatoms selected independently from O, S, and N, said heterocyclic ring being substituted with 0-4 R¹⁹,

20 C₁-C₆ alkyl substituted with a 5-10 membered heterocyclic ring system having 1-3 heteroatoms selected independently from O, S, and N, said heterocyclic ring being substituted with 0-4 R¹⁹;

R^{18b} is selected from R^{18a} or H;

25 R¹⁹ is selected from H, halogen, CF₃, CN, NO₂, NR¹²R¹³, C₁-C₈ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl, aryl(C₁-C₆ alkyl)-, C₁-C₆ alkoxy, or C₁-C₄ alkoxy carbonyl;

30 R²⁰ and R²¹ are each independently selected from H, C₁-C₁₀ alkyl, CO₂R⁵, C(=O)R^{5a}, CONR⁵R^{5a}, NR⁵C(=O)R^{5a}, NR¹²R¹³, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylmethyl, C₆-C₁₀ aryl, or C₇-C₁₁ arylalkyl;

R^{22} is selected from C_1-C_{10} alkyl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{15} cycloalkylalkyl, aryl, aryl(C_1-C_{10} alkyl)-; $C(=O)R^{5a}$, CO_2R^{5b} , $-C(=O)N(R^5)R^{5a}$, or a bond to X ;

5

m is 0-2;

n is 0-2;

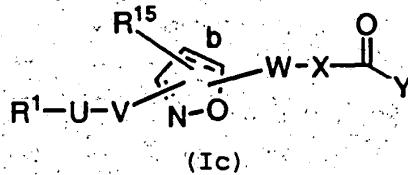
p is 1-2;

q is 1-7;

10 r is 0-3;

provided that n , q and r are chosen such that the number of atoms connecting R^1 and Y is in the range of 8-17.

15 [25] Preferred compounds of this embodiment are those compounds of Formula Ic:



20

wherein:

Z is selected from a bond (i.e. is absent), O , or S ;

25

R^2 is selected from H, aryl(C_1-C_{10} alkoxy)carbonyl, or C_1-C_{10} alkoxy carbonyl;

U is a single bond (i.e., U is not present);

30

X is $-CHR^{4a}-$;

R^5 is selected from H or C_1-C_{10} alkyl substituted with 0-6 R^{4b} ;

R⁶ and R⁷ are each independently selected from H, C₁-C₁₀ alkyl, hydroxy, C₁-C₁₀ alkoxy, nitro, C₁-C₁₀ alkylcarbonyl, -N(R¹²)R¹³, cyano, or halo;

5 R¹² and R¹³ are each independently selected from H, C₁-C₁₀ alkyl, C₁-C₁₀ alkoxy carbonyl, C₁-C₁₀ alkylcarbonyl, C₁-C₁₀ alkylsulfonyl, aryl(C₁-C₁₀ alkyl)sulfonyl, arylsulfonyl, or aryl, wherein said aryls are optionally substituted with
10 0-3 substituents selected from the group consisting of: C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, CF₃, and NO₂;

15 R¹⁵ is selected from H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, aryl, heteroaryl or C₁-C₁₀ alkoxy carbonyl, CO₂R⁵ or -C(=O)N(R⁵)R^{5a};

20 R¹⁶ is selected from:
-C(=O)-O-R^{18a},
-C(=O)-R^{18b},
-S(=O)₂-R^{18a};

R¹⁷ is selected from: H or C₁-C₄ alkyl;

25 R^{18a} is selected from:
C₁-C₈ alkyl substituted with 0-2 R¹⁹,
C₂-C₈ alkenyl substituted with 0-2 R¹⁹,
C₂-C₈ alkynyl substituted with 0-2 R¹⁹,
C₃-C₈ cycloalkyl substituted with 0-2 R¹⁹,
aryl substituted with 0-2 R¹⁹,
30 aryl(C₁-C₆ alkyl)- substituted with 0-2 R¹⁹,
a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, triazolyl, imidazolyl, benzofuranyl, indolyl, 35 indolinyl, quinolinyl, isoquinolinyl, isoxazolinyl,

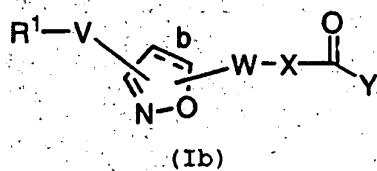
-84-

benzimidazolyl, piperidinyl, tetrahydrofuranyl,
 5 pyranyl, pyridinyl, 3H-indolyl, carbazolyl,
 pyrrolidinyl, piperidinyl, indolinyl, or
 morpholinyl, said heterocyclic ring being
 substituted with 0-2 R¹⁹;

10 C₁-C₆ alkyl substituted with a heterocyclic ring
 system selected from pyridinyl, furanyl, thiazolyl,
 thienyl, pyrrolyl, pyrazolyl, imidazolyl,
 15 isoxazoliny, benzofuranyl, indolyl, indolenyl,
 quinolinyl, isoquinolinyl, benzimidazolyl,
 piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl,
 3H-indolyl, indolyl, carbazole, pyrrolidinyl,
 piperidinyl, indolinyl, or morpholinyl, said
 heterocyclic ring being substituted with 0-2 R¹⁹.

[26] Further preferred compounds of this embodiment
 are compounds of Formula Ib:

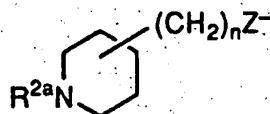
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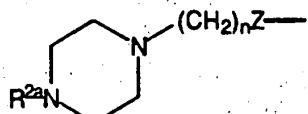
wherein:

25

R¹ is selected from: R²(R³)N-, R²NH(R²N=)C-,
 R²R³N(CH₂)_pZ-, R²NH(R²N=)CNH(CH₂)_pZ-,



, or



30

n is 0-1;

p' is 2-4;

p" is 4-6;

5 Z is selected from a bond (i.e. is absent) or O;

10 R³ is H or C₁-C₅ alkyl;

15 V is a single bond (i.e., V is not present), or
- (phenyl) -;

20 X is selected from:

-CH₂-;

-CHN(R¹⁶)R¹⁷-, or

-CHNR⁵R^{5a}-;

25 Y is selected from:

hydroxy;

C₁ to C₁₀ alkoxy;

methylcarbonyloxymethoxy-;

ethylcarbonyloxymethoxy-;

t-butylcarbonyloxymethoxy-;

cyclohexylcarbonyloxymethoxy-;

1-(methylcarbonyloxy)ethoxy-;

1-(ethylcarbonyloxy)ethoxy-;

20 1-(t-butylcarbonyloxy)ethoxy-;

1-(cyclohexylcarbonyloxy)ethoxy-;

i-propyloxycarbonyloxymethoxy-;

t-butyloxycarbonyloxymethoxy-;

1-(i-propyloxycarbonyloxy)ethoxy-;

30 1-(cyclohexyloxycarbonyloxy)ethoxy-;

1-(t-butyloxycarbonyloxy)ethoxy-;

dimethylaminoethoxy-;

diethylaminoethoxy-;

(5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;

35 (5-(t-butyl)-1,3-dioxacyclopenten-2-on-4-

yl)methoxy-;

(1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methoxy-;
1-(2-(2-methoxypropyl)carbonyloxy)ethoxy-;

R^{18a} is selected from:

5 C₁-C₄ alkyl substituted with 0-2 R¹⁹,
C₂-C₄ alkanyl substituted with 0-2 R¹⁹,
C₂-C₄ alkynyl substituted with 0-2 R¹⁹,
C₃-C₄ cycloalkyl substituted with 0-2 R¹⁹,
aryl substituted with 0-2 R¹⁹,
10 aryl(C₁-C₄ alkyl)- substituted with 0-2 R¹⁹,

a heterocyclic ring system selected from pyridinyl,
furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl,

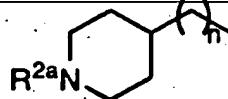
15 triazolyl, imidazolyl, benzofuranyl, indolyl,
indolinyl, quinolinyl, isoquinolinyl, isoxazolinyl,
benzimidazolyl, piperidinyl, tetrahydrofuranyl,
pyranyl, pyridinyl, 3H-indolyl, carbazolyl,
pyrrolidinyl, piperidinyl, indolinyl, or
morpholinyl, said heterocyclic ring being
20 substituted with 0-2 R¹⁹;

C₁-C₆ alkyl substituted with a heterocyclic ring
system selected from pyridinyl, furanyl, thiazolyl,
thienyl, pyrrolyl, pyrazolyl, imidazolyl,
25 isoxazolinyl, benzofuranyl, indolyl, indolenyl,
quinolinyl, isoquinolinyl, benzimidazolyl,
piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl,
3H-indolyl, indolyl, carbazole, pyrrolidinyl,
piperidinyl, indolinyl, or morpholinyl, said
30 heterocyclic ring being substituted with 0-2 R¹⁹.

[27] Further preferred compounds of this fifth
embodiment are compounds of Formula Ib wherein:

35 R¹ is R²NH(R²N=)C- or R²NH(R²N=)CNH- and V is phenyl or
pyridyl; or

R¹ is



, and V is a single bond (i.e. V

5 is absent)

n is 1-2;

R³ is H or C₁-C₅ alkyl;

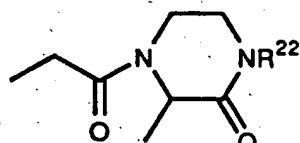
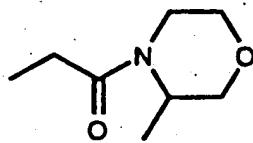
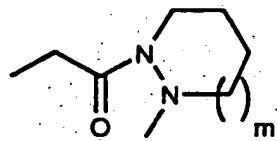
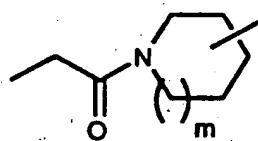
10 X is selected from:

-CH₂-,

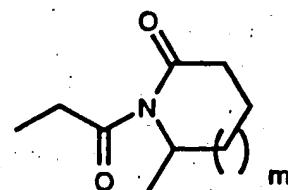
-CHN(R¹⁶)R¹⁷-, or

-CHNR⁵R^{5a}-;

15 W is selected from:



or



m is 1-3;

Y is selected from:

hydroxy;

C₁ to C₁₀ alkoxy;

5 methylcarbonyloxymethoxy-;

ethylcarbonyloxymethoxy-;

t-butylcarbonyloxymethoxy-;

cyclohexylcarbonyloxymethoxy-;

1-(methylcarbonyloxy)ethoxy-;

10 1-(ethylcarbonyloxy)ethoxy-;

1-(t-butylcarbonyloxy)ethoxy-;

1-(cyclohexylcarbonyloxy)ethoxy-;

i-propyloxycarbonyloxymethoxy-;

t-butyloxycarbonyloxymethoxy-;

15 1-(i-propyloxycarbonyloxy)ethoxy-;

1-(cyclohexyloxycarbonyloxy)ethoxy-;

1-(t-butyloxycarbonyloxy)ethoxy-;

dimethylaminoethoxy-;

diethylaminoethoxy-;

20 (5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;

(5-(t-butyl)-1,3-dioxacyclopenten-2-on-4-

yl)methoxy-;

(1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methoxy-;

1-(2-(2-methoxypropyl)carbonyloxy)ethoxy-;

25

R¹⁹ is H, halogen, C₁-C₄ alkyl, C₃-C₇ cycloalkyl,
cyclopropylmethyl, aryl, or benzyl;

30 R²⁰ and R²¹ are both H;

30

R²² is H, C₁-C₄ alkyl or benzyl.

[28] Specifically preferred compounds of this fifth embodiment are compounds of Formula Ib, or pharmaceutically acceptable salt forms thereof, selected from:

2-(R,S)-2-carboxymethyl-1-{5-(R,S)-N-[3-(4-
amidinophenyl)isoxazolin-5-yl acetyl]piperidine; 5
2-(R,S)-2-carboxymethyl-1-{5-(R,S)-N-[3-(4-
amidinophenyl)isoxazolin-5-yl acetyl]azepine; 10
2-(R,S)-2-carboxymethyl-1-{5-(R,S)-N-[3-(4-
amidinophenyl)isoxazolin-5-yl acetyl]pyrrolidine; 15
3-(R,S)-carboxymethyl-4-{5-(R,S)-N-[3-(4-
amidinophenyl)isoxazolin-5-yl acetyl]piperazine-2-
one; 20
6-(R,S)-carboxymethyl-1-{5-(R,S)-N-[3-(4-
amidinophenyl)isoxazolin-5-yl acetyl]piperidine-2-
one; 25
5-(R,S)-carboxymethyl-1-{5-(R,S)-N-[3-(4-
amidinophenyl)isoxazolin-5-yl acetyl]pyrrolidine-2-
one; 30
7-(R,S)-carboxymethyl-1-{5-(R,S)-N-[3-(4-
amidinophenyl)isoxazolin-5-yl acetyl]azetidine-2-
one; 35
2-(R,S)-carboxymethyl-1-{5-(R,S)-N-[3-(4-
amidinophenyl)isoxazolin-5-yl acetyl]pyrazolidine;
3-(R,S)-carboxymethyl-4-{5-(R,S)-N-[3-(4-
amidinophenyl)isoxazolin-5-yl acetyl]morpholine.

25 In the present invention it has been discovered
that the compounds of Formula I above are useful as
inhibitors of cell-matrix and cell-cell adhesion
processes. The present invention includes novel
compounds of Formula I and methods for using such
30 compounds for the prevention or treatment of diseases
resulting from abnormal cell adhesion to the
extracellular matrix which comprises administering to a
host in need of such treatment a therapeutically
effective amount of such compound of Formula I.
35 In the present invention it has also been
discovered that the compounds of Formula I above are,

-90-

useful as inhibitors of glycoprotein IIb/IIIa (GPIIb/IIIa). The compounds of the present invention inhibit the activation and aggregation of platelets induced by all known endogenous platelet agonists.

5

The present invention also provides pharmaceutical compositions comprising a compound of Formula I and a pharmaceutically acceptable carrier.

10

The compounds of Formula I of the present invention are useful for the treatment (including prevention) of thromboembolic disorders. The term "thromboembolic disorders" as used herein includes conditions involving platelet activation and aggregation, such as arterial or

15

venous cardiovascular or cerebrovascular thromboembolic disorders, including, for example, thrombosis, unstable angina, first or recurrent myocardial infarction, ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, venous thrombosis, deep vein

20

thrombosis, thrombophlebitis, arterial embolism, coronary and cerebral arterial thrombosis, myocardial infarction, cerebral embolism, kidney embolisms, pulmonary embolisms, or such disorders associated with diabetes, comprising administering to a mammal in need 25 of such treatment a therapeutically effective amount of a compound of Formula I described above.

30

The compounds of Formula I of the present invention may be useful for the treatment or prevention of other diseases which involve cell adhesion processes, including, but not limited to, inflammation, bone degradation, rheumatoid arthritis, asthma, allergies, adult respiratory distress syndrome, graft versus host disease, organ transplantation rejection, septic shock, 35 psoriasis, eczema, contact dermatitis, osteoporosis, osteoarthritis, atherosclerosis, tumors, metastasis,

diabetic retinopathy, inflammatory bowel disease and other autoimmune diseases. The compounds of Formula I of the present invention may also be useful for wound healing.

5

The compounds of the present invention are useful for inhibiting the binding of fibrinogen to blood platelets, inhibiting aggregation of blood platelets, treating thrombus formation or embolus formation, or 10. preventing thrombus or embolus formation in a mammal. The compounds of the invention may be used as a medicament for blocking fibrinogen from acting at its receptor site in a mammal.

Compounds of the invention may be administered to 15 patients where prevention of thrombosis by inhibiting binding of fibrinogen to the platelet membrane glycoprotein complex IIb/IIIa receptor is desired. They are useful in surgery on peripheral arteries (arterial grafts, carotid endarterectomy) and in cardiovascular 20 surgery where manipulation of arteries and organs, and/or the interaction of platelets with artificial surfaces, leads to platelet aggregation and consumption, and where the aggregated platelets may form thrombi and thromboemboli. The compounds of the present invention 25 may be administered to these surgical patients to prevent the formation of thrombi and thromboemboli.

Extracorporeal circulation is routinely used during cardiovascular surgery in order to oxygenate blood. 30. Platelets adhere to surfaces of the extracorporeal circuit. Adhesion is dependent on the interaction between GPIIb/IIIa on the platelet membranes and fibrinogen adsorbed to the surface of the extracorporeal circuit. Platelets released from artificial surfaces 35 show impaired homeostatic function. The compounds of

-92-

the invention may be administered to prevent such ex vivo adhesion.

5. The compounds of the present invention may be used for other ex vivo applications to prevent cellular adhesion in biological samples.

Other applications of these compounds include prevention of platelet thrombosis, thromboembolism, and reocclusion during and after thrombolytic therapy and prevention of platelet thrombosis, thromboembolism and 10 reocclusion after angioplasty of coronary and other arteries and after coronary artery bypass procedures.

The compounds of the present invention may also be used to prevent myocardial infarction. The compounds of the present invention are useful as thrombolytics for the 15 treatment of thromboembolic disorders.

The compounds of the present invention can also be administered in combination with one or more additional therapeutic agents select from: anti-coagulant or 20 coagulation inhibitory agents, such as heparin or warfarin; anti-platelet or platelet inhibitory agents, such as aspirin, piroxicam, or ticlopidine; thrombin inhibitors such as boropeptides, hirudin or argatroban; or thrombolytic or fibrinolytic agents, such as 25 plasminogen activators, anistreplase, urokinase, or streptokinase.

The compounds of Formula I of the present invention can be administered in combination with one or more of the foregoing additional therapeutic agents, 30 thereby to reduce the doses of each drug required to achieve the desired therapeutic effect. Thus, the combination treatment of the present invention permits the use of lower doses of each component, with reduced adverse, toxic effects of each component. A lower 35 dosage minimizes the potential of side effects of the compounds, thereby providing an increased margin of

safety relative to the margin of safety for each component when used as a single agent. Such combination therapies may be employed to achieve synergistic or additive therapeutic effects for the treatment of 5 thromboembolic disorders.

By "therapeutically effective amount" it is meant an amount of a compound of Formula I that when administered alone or in combination with an additional 10 therapeutic agent to a cell or mammal is effective to prevent or ameliorate the thromboembolic disease condition or the progression of the disease.

By "administered in combination" or "combination therapy" it is meant that the compound of Formula I and 15 one or more additional therapeutic agents are administered concurrently to the mammal being treated. When administered in combination each component may be administered at the same time or sequentially in any order at different points in time. Thus, each component 20 may be administered separately but sufficiently closely in time so as to provide the desired therapeutic effect.

The term anti-coagulant agents (or coagulation inhibitory agents), as used herein, denotes agents that 25 inhibit blood coagulation. Such agents include warfarin (available as CoumadinTM) and heparin.

The term anti-platelet agents (or platelet inhibitory agents), as used herein, denotes agents that inhibit platelet function such as by inhibiting the 30 aggregation, adhesion or granular secretion of platelets. Such agents include the various known non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, sulindac, indomethacin, mefenamate, droxicam, diclofenac, sulfinpyrazone, and 35 piroxicam, including pharmaceutically acceptable salts or prodrugs thereof. Of the NSAIDS, aspirin

(acetylsalicyclic acid or ASA), and piroxicam. Piroxicam is commercially available from Pfizer Inc. (New York, NY), as Feldane™. Other suitable anti-platelet agents include ticlopidine, including 5 pharmaceutically acceptable salts or prodrugs thereof. Ticlopidine is also a preferred compound since it is known to be gentle on the gastro-intestinal tract in use. Still other suitable platelet inhibitory agents include thromboxane-A2-receptor antagonists and 10 thromboxane-A2-synthetase inhibitors, as well as pharmaceutically acceptable salts or prodrugs thereof.

The phrase thrombin inhibitors (or anti-thrombin agents), as used herein, denotes inhibitors of the serine protease thrombin. By inhibiting thrombin, 15 various thrombin-mediated processes, such as thrombin-mediated platelet activation (that is, for example, the aggregation of platelets, and/or the granular secretion of plasminogen activator inhibitor-1 and/or serotonin) and/or fibrin formation are disrupted. 20 Such inhibitors include boroarginine derivatives and boropeptides, hirudin and argatroban, including pharmaceutically acceptable salts and prodrugs thereof. Boroarginine derivatives and boropeptides include N-acetyl and peptide derivatives of boronic acid, such 25 as C-terminal α -aminoboronic acid derivatives of lysine, ornithine, arginine, homoarginine and corresponding isothiouronium analogs thereof. The term hirudin, as used herein, includes suitable derivatives or analogs of hirudin; referred to herein as hirulogs, such as 30 disulfatohirudin. Boropeptide thrombin inhibitors include compounds described in Kettner et al., U.S. Patent No. 5,187,157 and European Patent Application Publication Number 293 881 A2, the disclosures of which are hereby incorporated herein by reference. Other 35 suitable boroarginine derivatives and boropeptide thrombin inhibitors include those disclosed in PCT

Application Publication Number 92/07869 and European Patent Application Publication Number 471 651 A2, the disclosures of which are hereby incorporated herein by reference, in their entirety.

5 The phrase thrombolytics (or fibrinolytic) agents (or thrombolytics or fibrinolytics), as used herein, denotes agents that lyse blood clots (thrombi). Such agents include tissue plasminogen activator, anistreplase, urokinase or streptokinase, including 10 pharmaceutically acceptable salts or prodrugs thereof. Tissue plasminogen activator (tPA) is commercially available from Genentech Inc., South San Francisco, California. The term anistreplase, as used herein, refers to anisoylated plasminogen streptokinase 15 activator complex, as described, for example, in European Patent Application No. 028,489, the disclosures of which are hereby incorporated herein by reference herein, in their entirety. Anistreplase is commercially available as EminaseTM. The term urokinase, as used 20 herein, is intended to denote both dual and single chain urokinase, the latter also being referred to herein as prourokinase.

Administration of the compounds of Formula I of the invention in combination with such additional 25 therapeutic agent, may afford an efficacy advantage over the compounds and agents alone, and may do so while permitting the use of lower doses of each. A lower dosage minimizes the potential of side effects, thereby providing an increased margin of safety.

30 GPIIb/IIIa is known to be overexpressed in metastatic tumor cells. The compounds or combination products of the present invention may also be useful for the treatment, including prevention, of metastatic cancer.

35 The compounds of the present invention are also useful as standard or reference compounds, for example

as a quality standard or control, in tests or assays involving the binding of fibrinogen to platelet GPIIb/IIIa. Such compounds may be provided in a commercial kit, for example, for use in pharmaceutical 5 research involving GPIIb/IIIa. The compounds of the present invention may also be used in diagnostic assays involving platelet GPIIb/IIIa.

The compounds herein described may have 10 asymmetric centers. Unless otherwise indicated, all chiral, diastereomeric and racemic forms are included in the present invention. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such 15 stable isomers are contemplated in the present invention. It will be appreciated that compounds of the present invention that contain asymmetrically substituted carbon atoms may be isolated in optically active or racemic forms. It is well known in the art 20 how to prepare optically active forms, such as by resolution of racemic forms or by synthesis, from optically active starting materials. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific 25 stereochemistry or isomer form is specifically indicated.

When any variable (for example but not limited to, R², R⁴, R⁶, R⁷, R⁸, R¹², and R¹⁴, n, etc.) occurs more 30 than one time in any constituent or in any formula, its definition on each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R⁴, then said group may optionally be substituted with up to two R⁴ and R⁴ at each occurrence is selected 35 independently from the defined list of possible R⁴. Also, by way of example, for the group -N(R^{5a})₂, each of

the two R^{5a} substituents on N is independently selected from the defined list of possible R^{5a} . Similarly, by way of example, for the group $-C(R^7)_2-$, each of the two R^7 substituents on C is independently selected from the defined list of possible R^7 .

When a bond to a substituent is shown to cross the bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a bond joining a substituent to another group is not specifically shown or the atom in such other group to which the bond joins is not specifically shown, then such substituent may form a bond with any atom on such other group.

When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of Formula I, then such substituent may be bonded via any atom in such substituent. For example, when the substituent is piperazinyl, piperidinyl, or tetrazolyl, unless specified otherwise, said piperazinyl, piperidinyl, tetrazolyl group may be bonded to the rest of the compound of Formula I via any atom in such piperazinyl, piperidinyl, tetrazolyl group.

Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By stable compound or stable structure it is meant herein a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "substituted", as used herein, means that any one or more hydrogen on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms (for example, "C₁-C₁₀" denotes alkyl having 1 to 10 carbon atoms); "haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example 5 -C_vF_w where v = 1 to 3 and w = 1 to (2v+1)); "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge; "cycloalkyl" is intended to include saturated ring groups, including 10 mono-, bi- or poly-cyclic ring systems, such as: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and adamantyl; and "bicycloalkyl" is intended to include saturated bicyclic ring groups such as [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), 15 [2.2.2]bicyclooctane, and so forth. "Alkenyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any 20 stable point along the chain, such as ethenyl, propenyl and the like; and "alkynyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more triple carbon-carbon bonds which may occur in any stable point along the chain, 25 such as ethynyl, propynyl and the like. 30 The terms "alkylene", "alkenylene", "phenylene", and the like, refer to alkyl, alkenyl, and phenyl groups, respectively, which are connected by two bonds to the rest of the structure of Formula I. Such "alkylene", "alkenylene", "phenylene", and the like, may 35 alternatively and equivalently be denoted herein as

"-(alkyl)-", "-(alkylenyl)-" and "-(phenyl)-", and the like.

"Halo" or "halogen" as used herein refers to fluoro, chloro, bromo and iodo; and "counterion" is used 5 to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, sulfate and the like.

As used herein, "aryl" or "aromatic residue" is intended to mean phenyl or naphthyl; the term 10 "arylalkyl" represents an aryl group attached through an alkyl bridge.

As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3- to 7- 15 membered monocyclic or bicyclic or 7- to 14-membered bicyclic or tricyclic or an up to 26-membered polycyclic carbon ring, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, 20 cyclopentyl, cyclohexyl, phenyl, biphenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin).

As used herein, the term "heterocycle" or "heterocyclic" is intended to mean a stable 5- to 7- 25 membered monocyclic or bicyclic or 7- to 10-membered bicyclic heterocyclic ring which may be saturated, partially unsaturated, or aromatic, and which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, O 30 and S and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring 35 may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The

-100-

heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. Examples of such heterocycles include, but are not limited to, pyridyl (pyridinyl), 5 pyrimidinyl, furanyl (furyl), thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, benzothiophenyl, indolyl, indolenyl, isoxazolinyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2- 10 pyrrolidonyl, pyrrolinyl, tetrahydrofuranlyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl or octahydroisoquinolinyl, azocinyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thianthrenyl, pyranyl, isobenzofuranyl, 15 chromenyl, xanthenyl, phenoxythiinyl, 2H-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, isothiazolyl, isoxazolyl, oxazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, indolyl, 1H-indazolyl, purinyl, 4H-quinolizinyl, 20 isoquinolinyl, quinolinyl, phthalazinyl, naphthyridinyl, quinoxaliny, quinazolinyl, cinnolinyl, pteridinyl, 4aH-carbazole, carbazole, 8-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, phenarsazinyl, phenothiazinyl, furazanyl, phenoxyazinyl, 25 isochromanyl, chromanyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidinyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl or oxazolidinyl. Also included are fused ring and spiro 30 compounds containing, for example, the above heterocycles.

As used herein, the term "heteroaryl" refers to aromatic heterocyclic groups. Such heteroaryl groups are preferably 5-6 membered monocyclic groups or 8-10 membered fused bicyclic groups. Examples of such

-101-

heteroaryl groups include, but are not limited to pyridyl (pyridinyl), pyrimidinyl, furanyl (furyl), thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, indolyl, isoxazolyl, oxazolyl, pyrazinyl, pyrimidinyl, 5 pyridazinyl, benzofuranyl, benzothienyl, benzimidazolyl, quinolinyl, or isoquinolinyl.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein 10 the parent compound of Formula I is modified by making acid or base salts of the compound of Formula I. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts 15 of acidic residues such as carboxylic acids; and the like.

"Prodrugs" are considered to be any covalently bonded carriers which release the active parent drug 20 according to Formula I *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of the compounds of Formula I are prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine 25 manipulation or *in vivo*, to the parent compounds. Prodrugs include compounds of Formula I wherein hydroxyl, amino, sulfhydryl, or carboxyl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, 30 amino, sulfhydryl, or carboxyl group respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of Formula I, and the like. Examples of representative carboxyl and 35 amino prodrugs are included under the definition of R², R³, and Y.

-102-

The pharmaceutically acceptable salts of the compounds of Formula I include the conventional non-toxic salts or the quaternary ammonium salts of the compounds of Formula I formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, 10 propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, 15 oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the compounds of Formula I which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts are 20 prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base in a suitable solvent or various combinations of solvents.

The pharmaceutically acceptable salts of the acids of Formula I with an appropriate amount of a base, such as an alkali or alkaline earth metal hydroxide e.g. sodium, potassium, lithium, calcium, or magnesium, or an organic base such as an amine, e.g., dibenzylenediamine, trimethylamine, piperidine, 30 pyrrolidine, benzylamine and the like, or a quaternary ammonium hydroxide such as tetramethylammonium hydroxide and the like.

As discussed above, pharmaceutically acceptable salts of the compounds of the invention can be prepared 35 by reacting the free acid or base forms of these compounds with a stoichiometric amount of the

-103-

appropriate base or acid, respectively, in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred.

5 Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985; p. 1418, the disclosure of which is hereby incorporated by reference.

10 The disclosures of all of the references cited herein are hereby incorporated herein by reference in their entirety.

Synthesis

15 The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods 20 described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. All references cited herein are hereby 25 incorporated in their entirety herein by reference.

The following abbreviations are used herein:

	β -Ala	3-aminopropionic acid
30	Boc	tert-butyloxycarbonyl
	Boc ₂ O	di-tert-butyl dicarbonate
	BSTFA	<i>N,O</i> -bis(trimethylsilyl)trifluoromethylacetamide
	Cbz	benzyloxycarbonyl
35	DCC	1,3-dicyclohexylcarbodiimide
	DEAD	diethyl azodicarboxylate

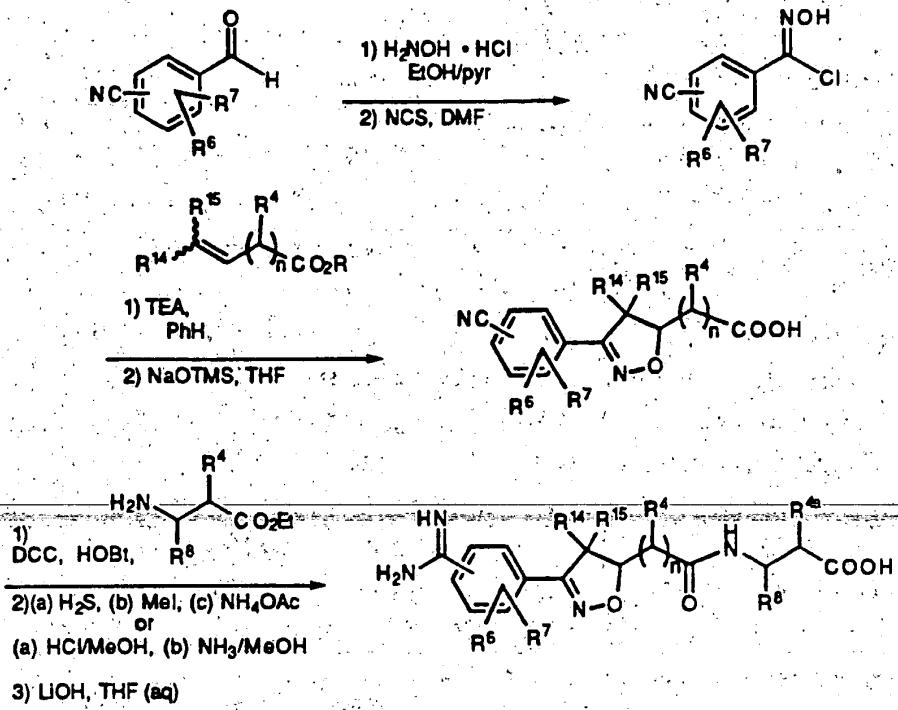
DEC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
DIEA	diisopropylethylamine
DCHA	dicyclohexylamine
5 DCM	dichloromethane
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
EtOAc	ethyl acetate
EtOH	ethyl alcohol
10 HOBT	1-hydroxybenzotriazole
IBCF	iso-butyl chloroformate
LAH	lithium aluminum hydride
NCS	N-chlorosuccinimide
NMM	N-methylmorpholine
15 PPh ₃	triphenylphosphine
pyr	pyridine
TBTU	2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TFA	trifluoroacetic acid
20 THF	tetrahydrofuran

25 A convenient method for the synthesis of the compounds of this invention utilizes a dipolar cycloaddition of nitrile oxides with appropriate dipolarophiles to prepare the isoxazoline rings present in compounds of Formula I (for reviews of 1,3-dipolar cycloaddition chemistry, see 1,3-Dipolar Cycloaddition Chemistry (Padwa, ed.), Wiley, New York, 1984; Kanemasa and Tsuge, *Heterocycles* 1990, **30**, 719).

30 Scheme I describes one synthetic sequence to the compounds of the second embodiment of this invention. An appropriately substituted hydroxylamine is treated with NCS in DMF according to the method of Liu, et al. (*J. Org. Chem.* 1980, **45**, 3916). The resulting hydroximinoyl chloride is then dehydrohalogenated *in situ* using TEA to give a nitrile oxide, which undergoes

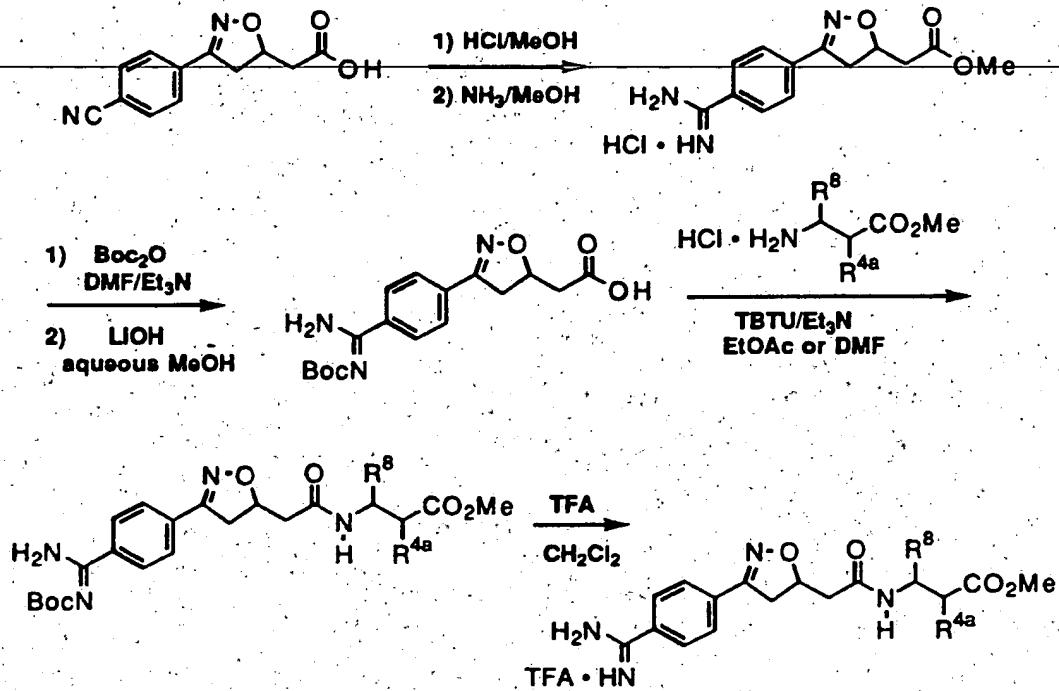
a 1,3-dipolar cycloaddition to a suitably substituted alkene to afford the isoxazoline. Alternatively, the oxime may be oxidatively chlorinated, dehydrochlorinated and the resulting nitrile oxide trapped by a suitable alkene under phase transfer conditions according to the method of Lee (Synthesis 1982, 508). Hydrolysis of the ester using conventional methods known to one skilled in the art of organic synthesis gives the desired acids. Intermediates containing alkali-sensitive functionality, such as nitrile, may be deesterified with excellent chemoselectivity using sodium trimethylsilylolate according to the procedure of Laganis and Ehenard (Tetrahedron Lett. 1984, 25, 5831). Coupling of the resulting acids to an appropriately substituted α - or β -amino ester using standard coupling reagents, such as DCC/HOBt, affords a nitrile-amide. The nitrile is then converted to the amidine via the imidate or thioimidate under standard conditions followed by ester saponification (LiOH, THF/H₂O).

Scheme I



5 An example of a related method of preparation for
compounds within the second embodiment of the present
invention is illustrated in Scheme Ia. Conversion of 3-
10 (4-Cyanophenyl)-isoxazolin-5-ylacetic acid to the
corresponding amidine, followed by protection as the
Boc-derivative and saponification provides 3-(4-Boc-
15 amidinophenyl)isoxazolin-5-ylacetic acid which is
coupled with β -amino acid esters as shown. Deprotection
provides the desired isoxazolinylacetyl- β -aminoalaninyl
esters. Saponification as described above gives the free
acids.

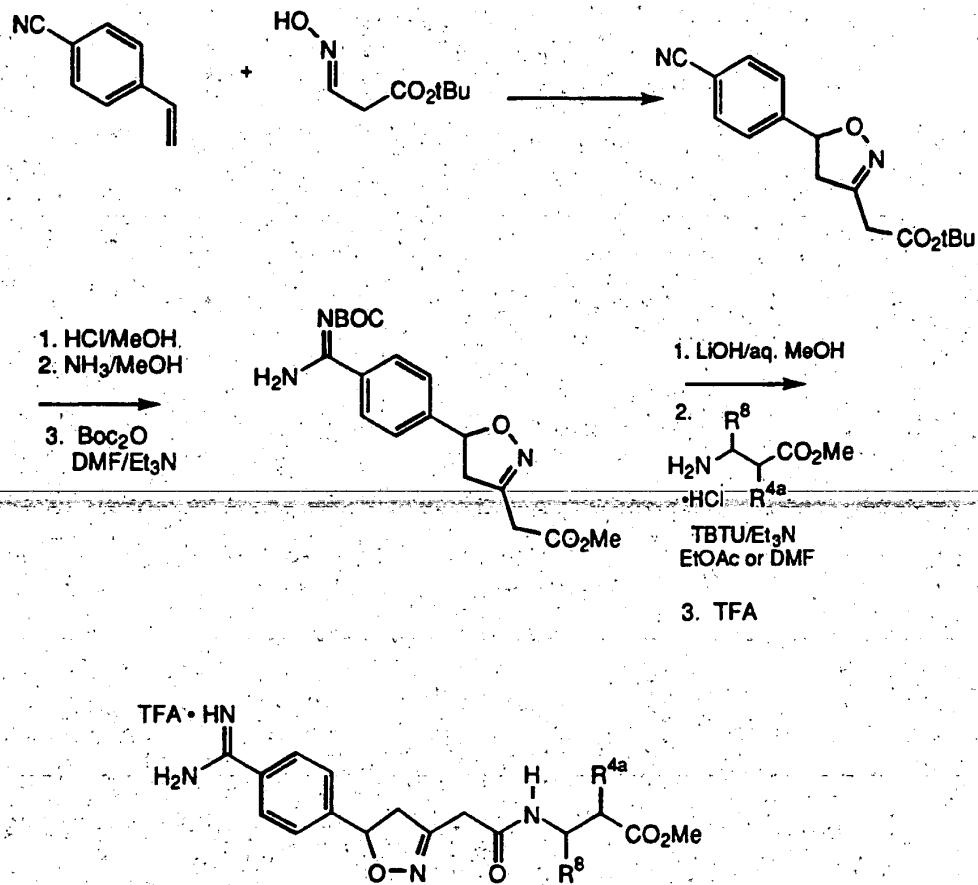
Scheme Ia



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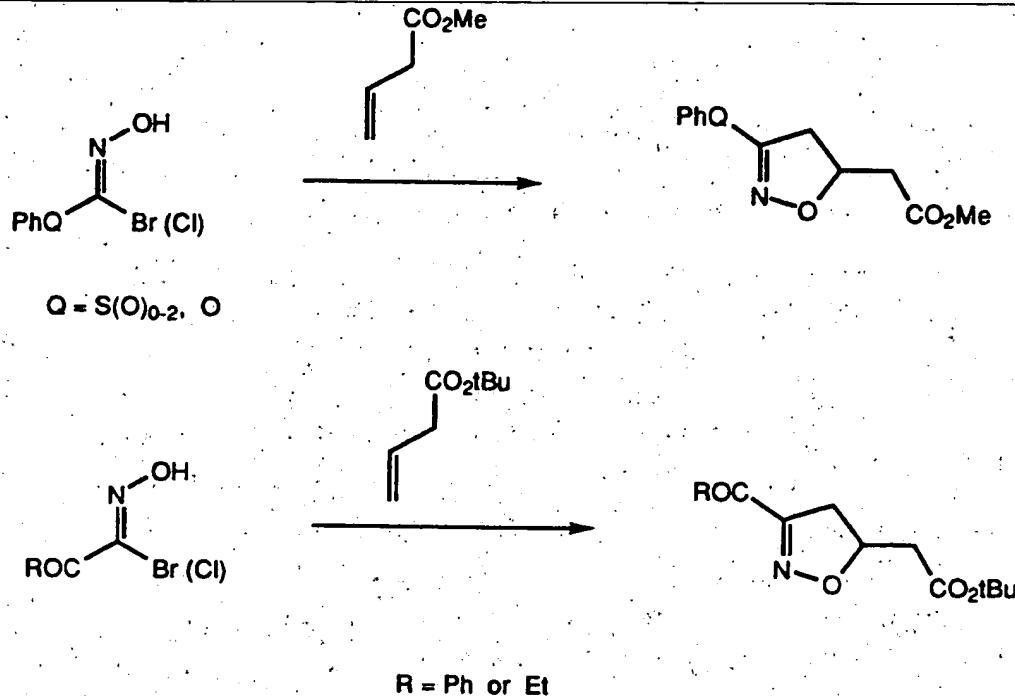
A further example of the synthesis of compounds within the second embodiment is shown in Scheme Ib. Cycloaddition of commercially available 4-cyanostyrene and *t*-butylformyloxime using the method described by 10 Gree et al. (Bioorganic and Med. Chem. Lett., 1994, 253) provides *t*-butyl [5-(4-cyanophenyl)isoxazolin-3-yl]acetate. Using the procedures described above, this 15 intermediate is converted to compounds of formula I wherein the isoxazoline ring is in the reverse orientation with respect to the compounds prepared via Schemes I and Ia.

Scheme Ib



5 Additional isoxazolinyl acetates useful as starting materials for the preparation of compounds of Formula I, wherein V is -(phenyl)-Q- and Q is other than a single bond, can be prepared by cycloaddition of a suitably substituted chloro or bromooxime with an ester of vinyl acetic acid as shown in Scheme Ic using literature methods or modifications thereof. (D. P. Curran & J. Chao, J. Org. Chem., 1988, 53, 5369-71; J. N. Kim & E. K. Ryu, Heterocycles, 1990, 31, 1693-97).

Scheme Ic



5 The compounds of the present invention where R^2 or R^3 is e.g. alkoxy carbonyl may be prepared by reacting the free amidines, amines or guanidines with an activated carbonyl derivative, such as an alkyl chloroformate. In compounds of the second embodiment, 10 the conversion of the free amines, amidines and guanidines to such acyl-nitrogen groups may optionally be performed prior to coupling an isoxazoline acetic acid with e.g. β -amino acids, as illustrated in Scheme Ia.

15 The compounds of the present invention wherein Y is an oxyalkoxy group, e.g. alkoxy carbonyloxyalkoxy, may be prepared by reacting a suitably protected carboxylic acid of Formula I with an e.g. an alkoxy carbonyloxyalkyl chloride in the presence of an iodide source, such as 20 tetrabutylammonium iodide or potassium iodide, and an acid scavenger, such as triethylamine or potassium

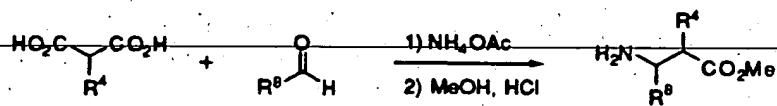
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carbonate, using procedures known to those skilled in the art.

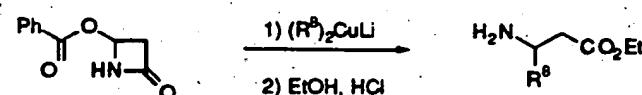
The appropriately substituted racemic β -amino acids may be purchased commercially or, as is shown in Scheme II, Method 1, prepared from the appropriate aldehyde, malonic acid and ammonium acetate according to the procedure of Johnson and Livak (J. Am. Chem. Soc. 1936, 58, 299). Racemic β -substituted- β -amino esters may be prepared through the reaction of dialkylcuprates or alkylolithiums with 4-benzyloxy-2-azetidinone followed by treatment with anhydrous ethanol (Scheme I, Method 2) or by reductive amination of β -keto esters as is described in WO9316038. (Also see Rico et al., J. Org. Chem. 1993, 58, 7948-51.) Enantiomerically pure β -substituted- β -amino acids can be obtained through the optical resolution of the racemic mixture or can be prepared using numerous methods, including: Arndt-Eistert homologation of the corresponding α -amino acids as shown in Scheme II, Method 3 (see Meier, and Zeller, Angew. Chem. Int. Ed. Engl. 1975, 14, 32; Rodriguez, et al. Tetrahedron Lett. 1990, 31, 5153; Greenlee, J. Med. Chem. 1985, 28, 434 and references cited within); and through an enantioselective hydrogenation of a dehydroamino acid as is shown in Scheme II, Method 4 (see Asymmetric Synthesis, Vol. 5, (Morrison, ed.) Academic Press, New York, 1985). A comprehensive treatise on the preparation of β -amino acid derivatives may be found in patent application WO 9307867, the disclosure of which is hereby incorporated by reference.

Scheme II

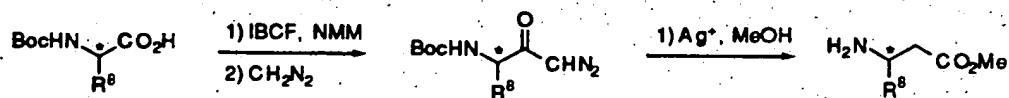
Method 1



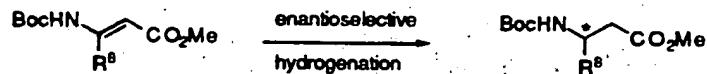
Method 2



Method 3



Method 4



5 The synthesis of N^2 -substituted diaminopropionic acid derivatives can be carried out via Hoffman rearrangement of a wide variety of asparagine derivatives as described in *Synthesis*, 266-267, (1981).

10 The appropriately substituted pyrrolidine-, piperidine- and hexahydroazepineacetic acids may be prepared using a number of methods. The pyrrolidines are conveniently prepared using an Arndt-Eistert homologation of the corresponding proline as shown in Scheme III, Method 1 (see Meier, and Zeller, *Angew. Chem. Int. Ed. Engl.* 1975, 14, 32; Rodriguez, et al. *Tetrahedron Lett.* 1990, 31, 5153; Greenlee, *J. Med. Chem.* 1985, 28, 434 and references cited within). The piperidines can be prepared by reduction of the corresponding pyridine as shown in Scheme III, Method 2.

15 The hexahydroazepines are prepared by reduction of the

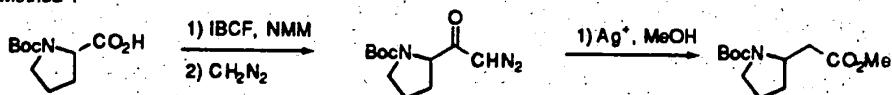
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corresponding vinylogous amide using sodium cyanoborohydride as depicted in Scheme III, Method 3.

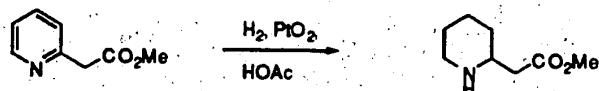
Scheme III

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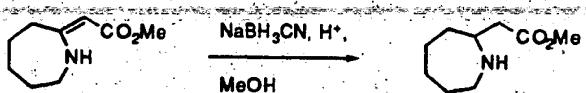
Method 1



Method 2



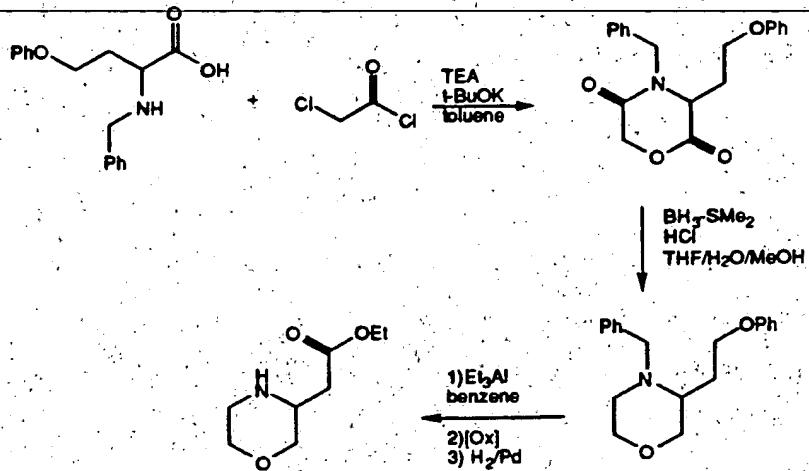
Method 3



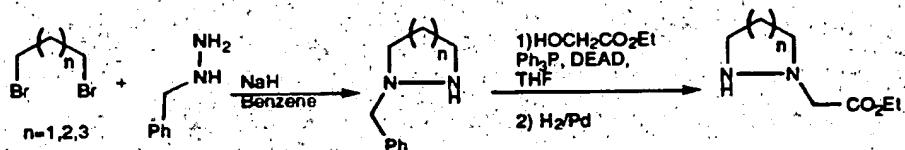
Many additional appropriately substituted heterocycles are available commercially or can be 10 readily modified by procedures known by one skilled in the art. Appropriately substituted morpholines can be prepared from amino acids via the sequence of steps depicted in Scheme IIIa, method 1 (see Brown, et. al. *J. Chem. Soc. Perkin Trans I*, 1987, 547.; Bettoni, et. al. *Tetrahedron* 1980, 36, 409. Clarke, F.H. *J. Org. Chem.* 1962, 27, 3251 and references therein.) N-ethoxycarbonylmethyl-1,2-diazaheterocycles are prepared by condensation of suitably substituted dibromides with benzylhydrazine followed by Mitsunobu reaction with 15 ethyl hydroxyacetate and deprotection as shown in Scheme IIIa, method 2 (see Kornet, et. al. *J. Pharm. Sci.* 1979, 68, 377.; Barcza, et. al. *J. Org. Chem.* 1976, 41, 1244 and references therein.)

Scheme IIIa

Method 1



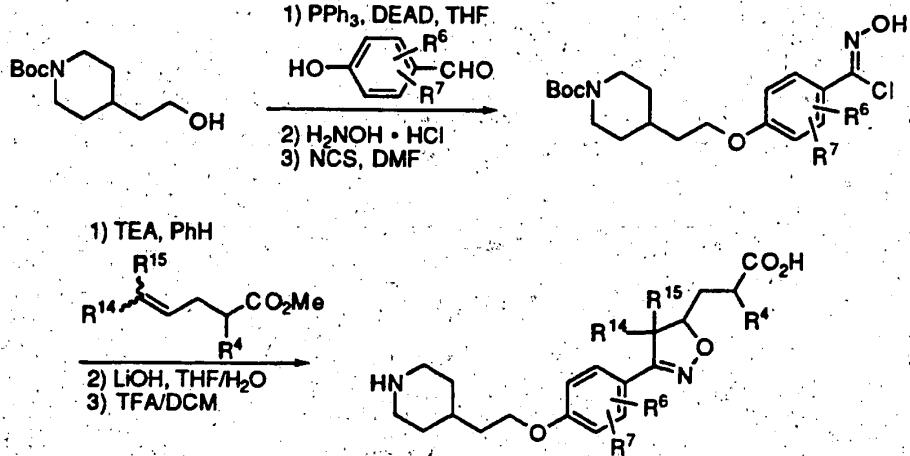
Method 2



5 A general synthetic protocol to the compounds of the first embodiment of this invention is depicted in Scheme IV. Coupling of a suitable Boc-protected amino alcohol to an appropriately substituted phenol under Mitsunobu conditions (see Mitsunobu, *Synthesis* 1981, 1)
 10 is followed by oximation using hydroxylamine hydrochloride in 1:1 ethanol/pyridine. Isoxazoline formation, ester saponification and Boc-deprotection (33% TFA/DCM) then affords the compounds of this invention in good overall yield.

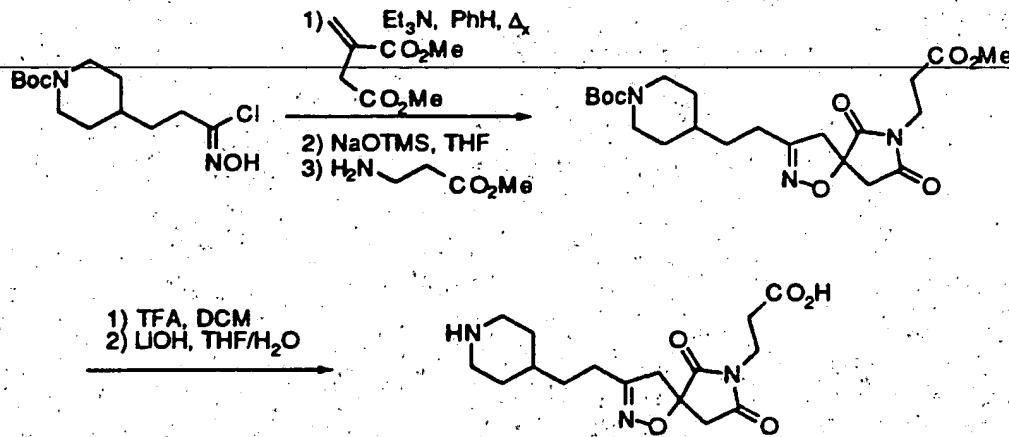
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Scheme IV



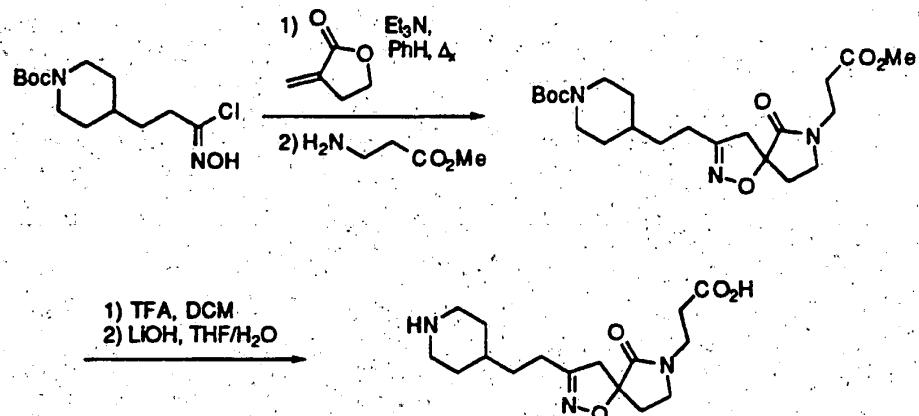
5 The synthesis of the spiro-fused isoxazolinyl imides of the third embodiment of the present invention is exemplified by the general protocol depicted in Scheme V. Dipolar cycloaddition of an oximinoyl chloride with a α -methylene diester affords an 10 isoxazolinyl diester, which is deesterified using the silanolate method. Dehydration to the anhydride according to Ishihara, et al. (Chem. Pharm. Bull. 1992, 40, 1177-85) followed by imide formation using an appropriately substituted amino ester affords the 15 spirocycle. Alternatively, the imide may be prepared directly from the isoxazoline diester according to Culbertson, et al. (J. Med. Chem. 1990, 33, 2270-75). Amidine formation or Boc deprotection followed by ester saponification then affords the compounds of this 20 invention in good overall yield.

Scheme V



5 The synthesis of the spiro-fused isoxazolinyl amides of the third embodiment of the present invention is exemplified by the general protocol depicted in Scheme VI. Dipolar cycloaddition of an oximinoyl chloride with a α -methylene lactone affords the 10 isoxazolinyl lactone, which is reacted with an appropriate amino ester to afford the amide (see *The Chemistry of the Amides* (Zabicky, ed.), p. 96, Interscience, New York, 1970; Prelog, et al., *Helv. Chim. Acta* 1959, **42**, 1301; Inubushi, et al., *J. Chem. Soc., Chem. Commun.* 1972, 1252). Amidine formation or 15 Boc deprotection followed by ester saponification then affords the compounds of this invention in good overall yield.

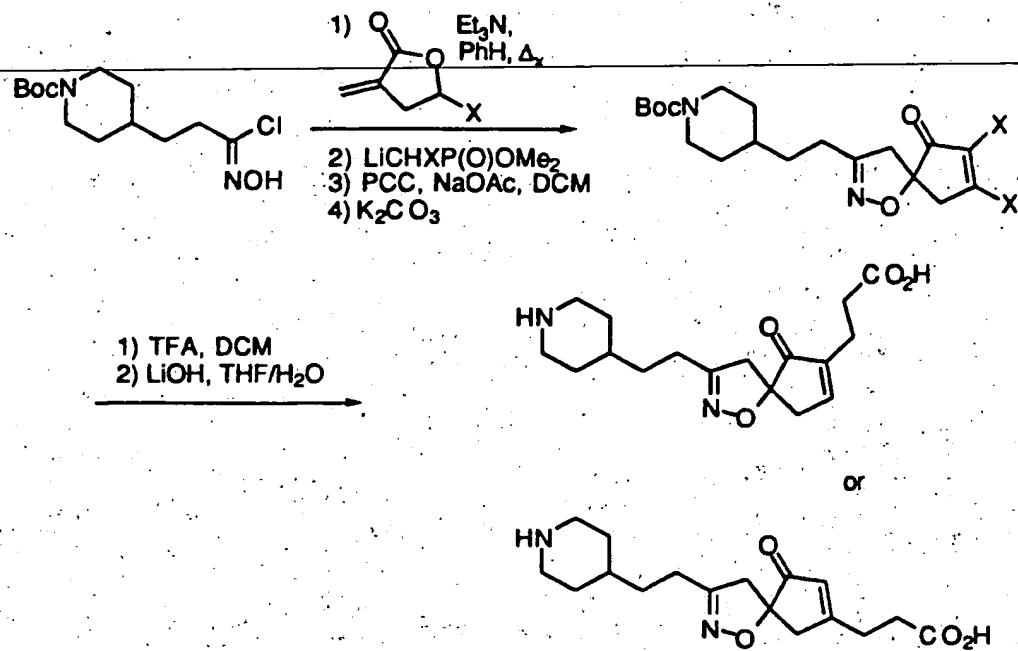
Scheme VI



5 The synthesis of the spiro-fused isoxazolinyl cycloalkenes of the third embodiment of the present invention is exemplified by the general protocol depicted in Scheme VII. Dipolar cycloaddition of an oximinoyl chloride with an appropriately substituted α -methylene lactone affords the isoxazolinyl lactone. The 10 lactone is then reacted with an appropriate lithium dimethyl alkylphosphonate, followed by PCC oxidation. The resulting diketophosphonate undergoes an intramolecular Wittig reaction in the presence of 15 $K_2CO_3/18$ -crown-6 according to the method described by Lim and Marquez (*Tetrahedron Lett.* 1983, **24**, 5559). Amidine formation or Boc deprotection followed by ester saponification then affords the compounds of this invention in good overall yield.

20

Scheme VII



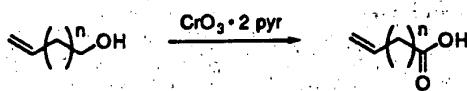
5 The dipolarophiles used to prepare the compounds of this invention may be prepared by numerous methods. The ω -alkenoic ester class of dipolarophile may be purchased commercially or prepared by oxidation of the corresponding ω -alkenols by the method of Corey and 10 Schmidt (Tetrahedron Lett. 1979, 399, Scheme VIII, Method 1). The α -methylene diester and α -methylene lactone class of dipolarophile may be purchased commercially or can be prepared by numerous methods from the corresponding diester (see Osbond, J. Chem. Soc. 15 1951, 3464; Ames and Davey, J. Chem. Soc. 1958, 1794; Vig, et al., Ind. J. Chem. 1968, 6, 60; Grieco and Hiroi, J. Chem. Soc., Chem. Commun. 1972, 1317, Scheme VIII, Method 2). The 3-(styryl)propionic ester class of dipolarophile may be prepared by palladium-catalyzed 20 cross coupling of the appropriately substituted bromo- or iodohydrocinnamic acid to a vinylmetal species according to methods cited within Mitchell (Synthesis

1992, 803) and Stille (Angew. Chem. Int. Ed. Engl. 1986, 25, 508, Scheme VIII, Method 3).

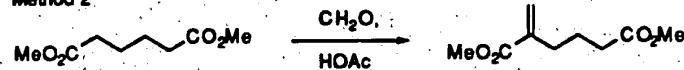
Scheme VIII

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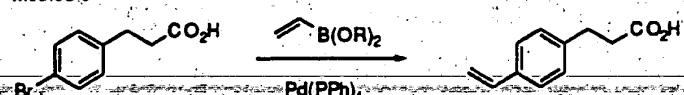
Method 1



Method 2



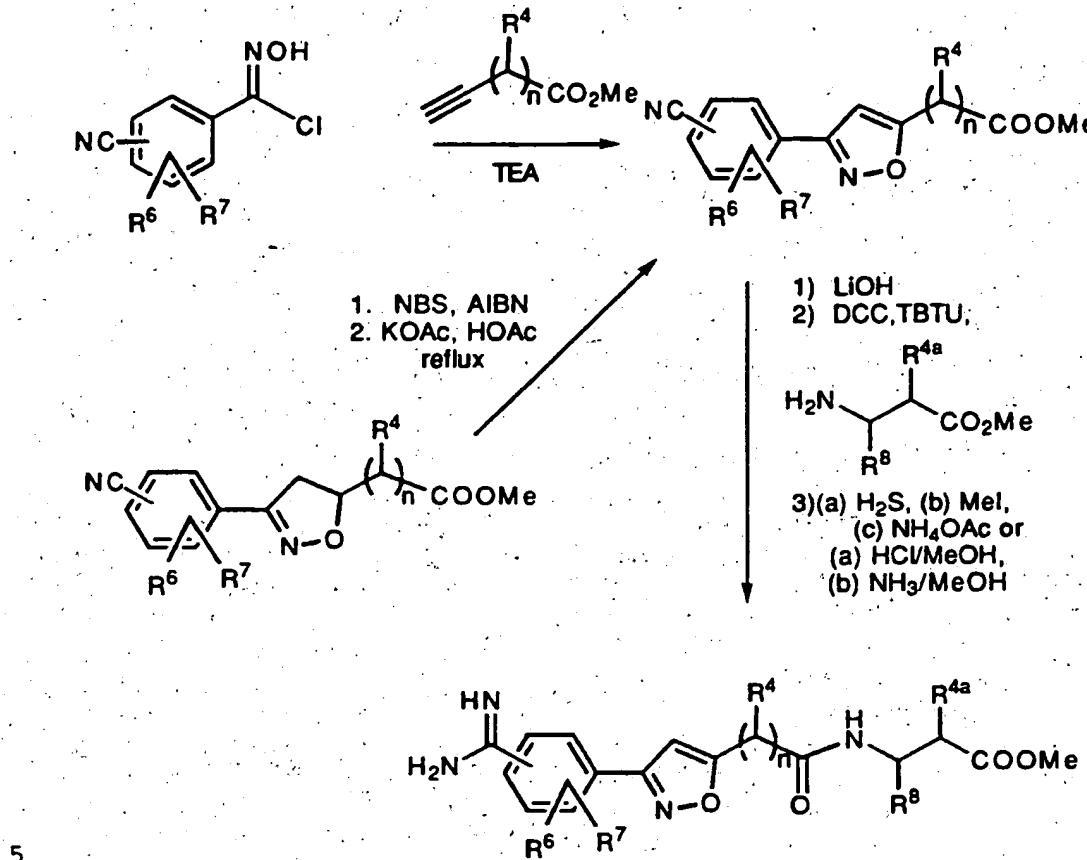
Method 3



Compounds of formula I wherein b is a double bond can be prepared using one of the routes depicted in

10 Scheme IX. Bromination followed by subsequent dehydrobromination of a suitably substituted methyl 3-(cyanophenyl)isoxazolin-5-ylacetate, prepared as described above, using the method of Elkasaby & Salem (Indian J. Chem., 1980, 19B, 571-575) provides the 15 corresponding isoxazole intermediate. Alternately, this intermediate can be obtained by 1,3-dipolar cycloaddition of a cyanophenyl nitrile oxide (prepared from the corresponding chlorooxime as described in Scheme I) with an appropriate alkyne to give the 20 isoxazole directly. Hydrolysis of the ester using conventional methods known to one skilled in the art of organic synthesis gives the acetic acids. Coupling of the resulting acids to an appropriately substituted α - or β -amino ester using standard coupling reagents, such 25 as TBTU, affords a nitrile-amide. The nitrile is then converted to the amidine via the imidate or thioimidate under standard conditions to give the prodrug esters. Saponification gives the acids.

Scheme IX



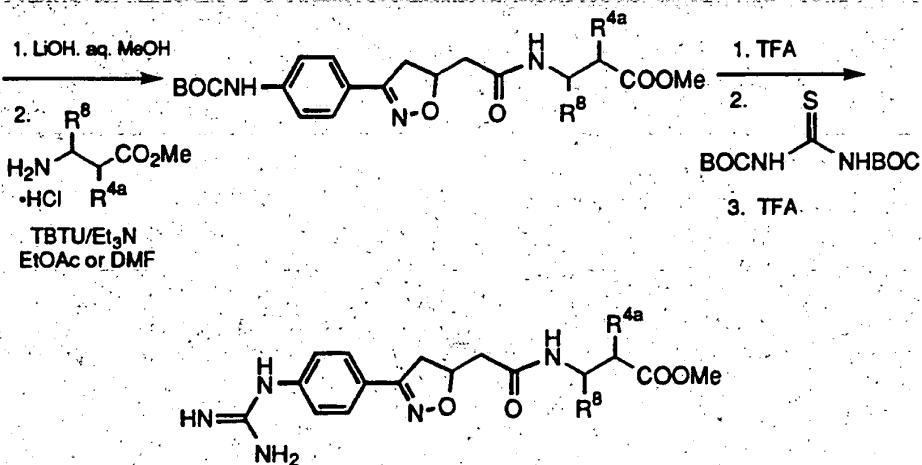
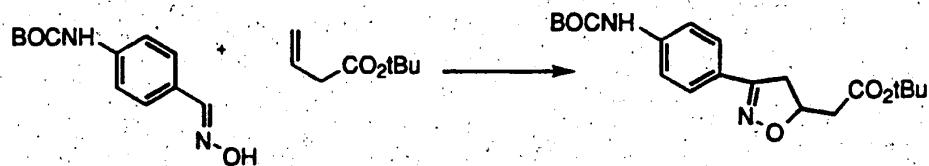
Compounds of Formula I wherein R^1 is $(\text{R}^2)(\text{R}^3)\text{N}(\text{R}^2\text{N}=\text{)CN}(\text{R}^2)-$ and V is phenylene are prepared as illustrated in Scheme X. Cycloaddition of an 10 appropriately N-protected aminophenylaldoxime with vinyl acetic acid, t-butyl ester, using the conditions described above provides t-butyl [3-(4-t-butyloxycarbonylaminophenyl)isoxazolin-5-yl]acetate. 15 Hydrolysis of the ester with lithium hydroxide provides the free acid which can be coupled with a suitably substituted methyl 3-aminopropionate as previously described. After deprotection, the aniline is converted

-120-

to the corresponding guanidine using the method described by Kim et al. (Tetrahedron Lett., 1993, 48, 7677). A final deprotection step to remove the BOC groups provides guanidino compounds of Formula I.

5

Scheme X



10

The compounds of this invention and their preparation can be further understood by the following procedures and examples, which exemplify but do not constitute a limit of their invention.

15

Example 1

3-[4-(2-Piperidin-4-yl)ethoxyphenyl]-5-(5R,S)-isoxazolin-5-ylacetic Acid, Trifluoroacetic Acid Salt

-121-

Part A. Preparation of 2-(4-N-t-Butyloxycarbonylpiperidin-4-yl)ethanol

This material was prepared from 4-piperidine-2-
5 ethanol according to European Patent Application
Publication Number 478363 A2.

Part B. 4-[(2-N-t-Butyloxycarbonylpiperidin-4-yl)ethoxy]benzaldehyde

10 To a solution of 2-(4-N-t-Butyloxycarbonylpiperidin-4-yl)ethanol (7.71 g, 33.6 mmol), 4-hydroxybenzaldehyde (4.11 g, 33.6 mmol) and PPh_3 (8.82 g, 33.6 mmol) in THF (60 mL) at -20 °C was added a solution of DEAD (5.3 mL, 33.7 mmol) in THF (30 mL) over 2 hours. During the addition, a deep red solution resulted, which changed to a golden color upon warming to room temperature overnight (18 hours). At this time the solution was concentrated and redissolved in EtOAc. It was then washed with water, 0.1M HCl, 1M NaOH, sat. NaCl and dried (MgSO_4). Concentration gave a solid (~20 g), which was purified using flash chromatography (10-20-30-40-50% EtOAc/hexanes step gradient), affording 7.82 g (70%) of the desired ether after pumping to constant weight; mp 76.4-79.7 °C; ^1H NMR (300 MHz, CDCl_3) δ 9.88 (s 1H), 7.83 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 8.4 Hz, 2H), 4.10 (bd, J = 12.8 Hz, 2H), 4.04 (t, J = 6.6 Hz, 2H), 2.69 (bt, 2H), 1.84 (m, 2H), 1.70 (bd J = 14.3 Hz, 2H), 1.46 (s, 9H, overlapped with m, 2H), 1.10 (m, 2H).

30 Part C. 4-[(2-N-t-Butyloxycarbonylpiperidin-4-yl)ethoxy]benzaldoxime

To a solution of 4-[(2-N-t-butyloxycarbonylpiperidin-4-yl)ethoxy]benzaldehyde (3.16 g, 9.48 mmol) in MeOH

-122-

(20 mL) was added hydroxylamine hydrochloride (1.27 g, 18.3 mmol) and 2M NaOH (7 mL, 14 mmol). The resulting suspension was stirred overnight at room temperature (18 hours). The mixture was brought to pH 4 using 1M HCl, followed by filtration and water wash. The crystals were dried under vacuum over P₂O₅, affording 2.88 g (87%); mp: 114.4-116.1 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.09 (s, 2H), 7.51 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 4.10 (b, 2H), 4.03 (t, J = 6.2 Hz 2H), 2.71 (bt, 2H), 1.73 (m, 4H), 1.46 (s, 9H), 1.19 (m, 2H).

Part D. 4-[(2-N-t-Butyloxycarbonylpiperidin-4-yl)ethoxy]benzaldoximoyl Chloride

15 To a solution of 4-[(2-N-t-butyloxycarbonylpiperidin-4-yl)ethoxy]benzaldoxime (955 mg, 2.74 mmol) in DMF (5 mL) was added NCS (366 mg, 2.74 mmol) in 3 portions. After 3 hours, the solution was diluted with EtOAc and washed with water, sat. NaCl, dried (MgSO₄) and concentrated. The resulting solid was crystallized from ether/hexanes to give 548 mg (52%) of the oximinoyl chloride; mp: 119.3-119.9 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.37 (bs 1H), 7.77 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 4.12 (bd, J = 13.2 Hz, 2H), 4.04 (t, J = 6.2 Hz 2H), 2.72 (bt, J = 12.1 Hz, 2H), 1.70 (m, 5H), 1.46 (s, 9H), 1.10 (m, 2H).

Part E. Methyl 3-[(4-[(2-N-t-Butyloxycarbonylpiperidin-4-yl)ethoxy]phenyl)-(5R,S)-isoxazolin-5-yl]acetate

30 To a solution of 4-[(2-N-t-butyloxycarbonylpiperidin-4-yl)ethoxy]benzaldoximoyl chloride (400 mg, 1.045 mmol) and methyl 3-butenoate (200 mg, 2.00 mmol) was added TEA (0.15 mL, 1.1 mmol). The resulting suspension was heated at reflux for 5 hours, cooled to room temperature and diluted with EtOAc. It was then washed

-123-

with 0.1M HCl, water, sat. NaCl, dried (MgSO₄) and concentrated. The resulting solid was crystallized from DCM/hexanes to give 357 mg (77%) of the isoxazoline; mp: 139.1-140.9 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.59 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 5.08 (m, 1H), 4.10 (bd, J = 13.2 Hz, 2H), 4.04 (t, J = 5.9 Hz 2H), 3.73 (s, 3H), 3.53 (dd, J = 16.5, 10.1 Hz, 1H), 3.10 (dd, J = 16.8, 7.1 Hz, 1H), 2.88 (dd, J = 16.1, 5.9 Hz, 1H), 2.71 (bt, J = 12.8 Hz, 2H), 2.64 (dd, J = 15.8, 7.7 Hz, 1H), 1.72 (m, 5H), 1.46 (s, 9H), 1.08 (m, 2H).

Part F. 3-[4-[(2-N-t-Butyloxycarbonylpiperidin-4-yl)ethoxy]phenyl]-(5R,S)-isoxazolin-5-ylacetic Acid

15 To a solution of methyl 3-[4-[(2-N-t-butyloxycarbonylpiperidin-4-yl)ethoxy]phenyl]-(5R,S)-isoxazolin-5-ylacetate (47 mg, 0.105 mmol) in THF (2 mL) was added 0.5M LiOH (1 mL, 0.5 mmol). The reaction was stirred at room temperature for 5 hours, then was acidified to pH 3 using 0.1M HCl. The mixture was washed with DCM and the combined organic fraction dried (MgSO₄) and concentrated. The resulting solid was crystallized from EtOAc/hexanes to give 34 mg (74%) of the carboxylic acid; mp: 169.1-170.6 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.60 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 5.10 (m, 1H), 4.08 (bd, 2H, overlapped with t, J = 5.9 Hz 2H), 3.55 (dd, J = 16.5, 10.2 Hz, 1H), 3.11 (dd, J = 16.8, 7.0 Hz, 1H), 2.93 (dd, J = 16.1, 6.2 Hz, 1H), 2.71 (m, 3H), 2.00 (m, 2H), 1.72 (m, 5H), 1.46 (s, 9H).

30 Part G. 3-[4-(2-Piperidin-4-yl)ethoxyphenyl]-(5R,S)-isoxazolin-5-ylacetic Acid. Trifluoroacetic Acid Salt

35 To a solution of 3-[4-[(2-N-t-Butyloxycarbonylpiperidin-4-yl)ethoxy]phenyl]-(5R,S)-isoxazolin-5-ylacetic acid (53 mg, 0.12 mmol) in DCM (2 mL) was added TFA (1

-124-

mL, 13 mmol). After 1.5 hours, the product was crystallized by the addition of ether, affording 33 mg (60%) of the amino acid; mp: 142.4-143.1 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.59 (dd, J = 8.8, 2.6 Hz, 2H), 6.96 (dd, J = 8.8, 2.6 Hz, 2H), 5.03 (m, 1H), 4.10 (m, 2H), 3.55 (ddd, J = 16.8, 10.3, 2.2 Hz, 1H), 3.38 (bd, J = 12.4 Hz, 2H), 3.16 (ddd, J = 17.2, 7.7, 2.2 Hz, 1H), 2.98 (bt, J = 13.2 Hz, 2H), 2.69 (m, 2H), 2.01 (bd, J = 14.3 Hz, 2H), 1.91 (m, 1H), 1.80 (m, 2H), 1.46 (m, 2H).

-125-

Example 4

(2S)-(5R,S)-[3-[4-[(2-Piperidin-4-yl)ethoxy]phenyl]isoxazolin-5-yl]{{[(benzyloxy)carbonyllamino]acetate}}

Trifluoroacetic Acid Salt

5

Part A. Benzyl L-2-{{[(benzyloxy)carbonyllamino]-3-butenoate}}

This material was prepared from *N*-Cbz-L-glutamic acid α -benzyl ester according to Krol, et al. (*J. Org. Chem.* 1991, 728).

Part B. Benzyl (2S)-(5R,S)-[3-[4-[(2-N-t-Butyloxycarbonylpiperidin-4-yl)ethoxy]phenyl]isoxazolin-5-yl]{{[(benzyloxy)carbonyllamino]acetate}}

To a solution of 4-[(2-N-t-butyloxycarbonylpiperidin-4-yl)ethoxy]benzaldoxime (852 mg, 2.44 mmol) and benzyl L-2-{{[(benzyloxy)carbonyl]amino}-3-butenoate (612 mg, 1.88 mmol) in DCM (10 mL) was added 5% NaOCl (common household bleach, 4 mL, 2.8 mmol). The mixture was rapidly stirred at room temperature for 22 hours, after which time it was diluted with water and DCM. After separation of the layers, the aqueous was washed with DCM (3x). The combined organic extracts were dried (MgSO_4) and concentrated *in vacuo*, giving 1.4 g. Purification using flash chromatography (10% EtOAc/hexanes - 30% EtOAc/hexanes) then afforded 886 mg (70%) of an oily product as a 2.5 : 1 mixture of the 30 erythro and threo isomers; ^1H NMR (400 MHz, CDCl_3) δ 7.50 (m, 2H), 7.34 (m, 5H), 7.23 (m, 5H), 6.87 (d, J = 8.8 Hz, 2H), 5.47 (bd, 1H), 5.12 (m, 5H), 4.60 (m, 1H), 4.07 (m, overlapped with 4.03 (J = 6.1 Hz, 4H)), 3.36 (m, 2H), 2.71 (bt, J = 12.7 Hz, 2H), 1.70 (m, 5H), 1.45 (s,

-126-

9H), 1.18 (m, 2H); Anal. Calc. for C₃₈H₄₅N₃O₈: C, 67.93; H, 6.76; N, 6.26. Found: C, 67.95; H, 6.77; N, 6.17.

Part C. (2S)-(5R,S)-[3-[4-[(2-N-t-Butyloxycarbonylpiperidin-4-yl)ethoxy]phenyl]isoazolin-5-yl][(benzyloxy)carbonyllaminolacetic Acid

A solution of benzyl (2S)-(5R,S)-[3-[4-[(2-N-t-butyloxycarbonylpiperidin-4-yl)ethoxy]phenyl]isoazolin-5-yl][(benzyl-oxy)carbonyl]amino]acetate (875 mg, 1.302 mmol) in THF (5 mL) was saponified over 5 hours using 0.5M LiOH (3.5 mL) according to Example 1, Part F. To the crude product was added methanol, causing

crystallization of one of the diastereomers. Filtration

and pumping to constant weight gave 295 mg (39%); mp: 216.1 °C; ¹H NMR (400 MHz, DMSO-d₆, 80 °C). δ 7.50 (d, J = 8.9 Hz, 2H), 7.23 (s, 5H), 6.96 (d, J = 8.9 Hz, 2H), 6.17 (bs, 1H), 4.99 (m, 3H), 4.07 (t, J = 6.1 Hz, 2H), 3.90 (m, 3H), 3.35 (d, J = 9.3 Hz, 2H), 2.72 (bt, J = 12.4 Hz, 2H), 1.67 (m, 5H), 1.39 (s, 9H), 1.08 (m, 2H).

The filtrate was concentrated in vacuo and pumped until constant weight was achieved, giving 200 mg (26%) of the carboxylic acids as a mixture of erythro- and threo-isomers; TLC (silica gel 60, 20% MeOH/CHCl₃). R_f = 0.23,

Mass Spectrum (ESI, e/z, relative abundance) 582 (M + H)⁺, 32%; 526 (M - C₄H₉ + H₂)⁺, 100%; 482 (M - Boc + H₂)⁺, 91%.

Part D. (2S)-(5R,S)-[3-[4-[(2-Piperidin-4-yl)ethoxy]phenyl]isoazolin-5-yl][(benzyloxy)carbonyllaminolacetic Acid (isomer A)

(2S)-(5R,S)-[3-[4-[(2-N-t-Butyloxycarbonylpiperidin-4-yl)ethoxy]phenyl]isoazolin-5-yl][(benzyloxy)carbonyl]amino]acetate (23 mg, 0.039 mmol) was Boc-deprotected using 33% TFA/DCM according to Example 1,

-127-

Part G, giving 15 mg (79%); mp: 302 °C (dec); ¹H NMR (400 MHz, DMSO-d₆, 60 °C) δ 7.57 (d, J = 8.8 Hz, 2H), 7.30 (s, 5H), 6.99 (d, J = 8.8 Hz, 2H), 5.05 (s, 2H, coincident with m, 1H), 4.35 (d, J = 4.9 Hz, 1H), 4.09 5 (t, J = 6.1 Hz, 2H), 3.52 (dd, J = 17.3, 10.7 Hz, 1H), 3.26 (m, 3H), 2.88 (dt, J = 12.7, 2.7 Hz, 2H), 1.88 (bd, J = 14.4 Hz, 2H), 1.80 (m, 1H), 1.72 (m, 2H), 1.38 (m, 2H).

10 Part D'. (2S)-(5R,S)-[3-[4-[(2-Piperidin-4-yl)ethoxy-
yl]phenyl]isoxazolin-5-yl][(benzyloxy)carbonylaminolla-
cetic Acid. Trifluoroacetic Acid Salt (isomer B)

15 (2S)-(5R,S)-[3-[4-[(2-N-t-Butyloxycarbonylpiperi-
din-4-yl)ethoxy]phenyl]isoxazolin-5-yl][(benzyloxy)car-
bonyl]amino]acetic acid (177 mg, 0.304 mmol) was Boc-
deprotected using 33% TFA/DCM according to Example 1,
Part G, giving 3 mg (2%) of the TFA salt; mp: >400 °C;
1H NMR (400 MHz, DMSO-d₆, 60 °C) δ 8.48 (bs, 0.5H), 8.15
20 (bs, 0.5H), 7.55 (d, J = 8.9 Hz, 2H), 7.30 (m, 5H), 6.97
(d, J = 8.9 Hz, 2H), 5.05 (s, 2H), 4.96 (m, 1H), 4.33
(m, 1H), 4.07 (t, J = 6.3 Hz, 2H), 3.38 (m, 2H), 3.26
(bd, J = 12.0 Hz, 2H), 2.87 (m, 2H), 1.86 (bd, J = 14.2
Hz, 2H), 1.78 (m, 1H), 1.70 (apparent q, J = 6.3 Hz,
25 2H), 1.36 (bq, J = 13.2 Hz, 2H).

Example 6

3-(3-[4-(Piperidin-4-ylmethoxy)phenyl]-(5R,S)-isoxazol-
in-5-yl)propionic Acid. Trifluoroacetic Acid Salt

30 Part A. Ethyl N-t-Butyloxycarbonylpiperidine-4-
carboxylate

35 To a stirred solution of ethyl isonipeptate (20.01 g, 0.1273 mol) in EtOAc (100 mL) at 0 °C was added dropwise a solution of Boc₂O (27.76 g, 0.1272 mol) in

-128-

EtOAc (50 mL). The mixture was allowed to warm to room temperature overnight. After 20 hours, the mixture was washed with water, 0.1M HCl, sat. NaHCO₃, sat. NaCl and dried (MgSO₄). Concentration and pumping under vacuum

5 to constant weight gave 32.54 g (99%) of the desired carbamate as a mobile oil; ¹H NMR (300 MHz, CDCl₃) δ 4.13 (q, J = 7.0 Hz, 2H), 4.03 (dm, J = 13.6 Hz 2H), 2.81 (m, 2H), 2.41 (m, 1H), 1.86 (dm, J = 13.6 Hz, 2H), 1.62 (m, 2H), 1.44 (s, 9H), 1.24 (t, J = 7.0 Hz, 3H).

10

Part B. N-t-Butyloxycarbonylpiperidin-4-ylmethanol

To a solution of ethyl *N*-t-butylloxycarbonylpiperidine-4-carboxylate (32.34 g, 0.1257 mol) in THF (100 mL) 15 at 0 °C was added dropwise 1M LAH in THF (87.9 mL, 0.0879 mol). After 2 hours, excess hydride was quenched by the addition of water (3.2 mL), 2M NaOH (3.2 mL) and water (10 mL). The mixture was filtered, washed with EtOAc and the filtrate washed with water, sat. NaCl, 20 dried (MgSO₄) and concentrated. Pumping to constant weight gave 22.72 g (84%); mp: 79.2-81.1 °C; ¹H NMR (300 MHz, CDCl₃) δ 4.12 (bd, J = 12.8 Hz 2H), 3.49 (d, J = 6.2 Hz, 2H), 2.68 (dt, J = 13.2, 1.8 Hz, 2H), 1.69 (m, 3H), 1.44 (s, 9H, overlapped with m, 1H), 1.14 (m, 2H).

25

Part C. 4-(N-t-Butyloxycarbonylpiperidin-4-ylmethoxy)-benzaldehyde

To *N*-t-butylloxycarbonylpiperidin-4-ylmethanol (7.87 g, 36.5 mmol), *p*-hydroxybenzaldehyde (4.46 g, 36.5 mmol) 30 and PPh₃ (9.59 g, 36.5 mmol) in THF (100 mL) at -20 °C was added DEAD (5.75 mL, 36.5 mmol) in THF (50 mL) according to Example 1, Part B, affording 8.14 g (70%); mp: 115.6-116.8 °C; ¹H NMR (300 MHz, CDCl₃) δ 9.86 (s, 1H), 7.81 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 4.15 (bd, J = 13.2 Hz 2H), 3.87 (d, J = 6.6 Hz, 2H).

-129-

2.74 (dt, $J = 12.4, 1.8$ Hz, 2H), 1.97 (m, 1H), 1.81 (bd, $J = 12.8$ Hz, 2H), 1.45 (s, 9H), 1.27 (dq, $J = 12.1, 4.0$ Hz, 2H).

5 Part D. 4-(N-t-Butyloxycarbonylpiperidin-4-ylmethoxy)-benzaldoxime

A mixture of 4-(N-t-butyloxycarbonylpiperidin-4-ylmethoxy)benzaldehyde (3.16 g, 9.89 mmol) and 10 hydroxylamine hydrochloride (1.27 g, 18.3 mmol) in 9:1 MeOH/pyridine (30 mL) was heated at reflux for 18 hours. The mixture was cooled to room temperature and concentrated to dryness. The residue was dissolved in EtOAc and washed with 0.1M HCl (3x), water, sat. CuSO₄ 15 (2x), water, sat. NaCl, dried (MgSO₄) and concentrated, giving 3.19 g (96%) of the oxime; mp: 140.1-141.8 °C; ¹H NMR (300 MHz, CDCl₃) δ 8.07 (s, 1H), 7.48 (d, $J = 8.8$ Hz, 2H), 6.86 (d, $J = 8.8$ Hz, 2H), 4.14 (bs, 2H), 3.80 (d, $J = 6.2$ Hz, 2H), 2.71 (bt, $J = 12.4$ Hz, 2H), 1.95 (m, 1H), 20 1.80 (bd, $J = 12.4$ Hz, 2H), 1.45 (s, 9H), 1.26 (m, 2H).

Part E. 4-(N-t-Butyloxycarbonylpiperidin-4-ylmethoxy)-benzaldoximoyl Chloride

25 4-(N-t-Butyloxycarbonylpiperidin-4-ylmethoxy)-benzaldoxime (3.19 g, 9.54 mmol) in DMF (10 mL) was reacted with NCS (1.27 g, 9.51 mmol) for 18 hours according to Example 1, Part D to afford the hydroximinoyl chloride (1.17 g, 33%); mp: 178.0-179.8 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.75 (d, $J = 9.0$ Hz, 2H), 6.86 (d, $J = 9.0$ Hz, 2H), 4.17 (bd, $J = 12.4$ Hz, 2H), 3.80 (d, $J = 6.2$ Hz, 2H), 2.74 (dt, $J = 12.8, 1.8$ Hz, 2H), 1.95 (m, 1H), 1.81 (bd, $J = 12.1$ Hz, 2H), 1.46 (s, 9H), 1.27 (dq, $J = 12.5, 4.0$ Hz, 2H).

-130-

Part F. Methyl 3-[3-[4-(N-t-Butyloxycarbonylpiperidin-4-ylmethoxy)phenyl]- (5R,S)-isoxazolin-5-yl]propionate

4-(N-t-Butyloxycarbonylpiperidin-4-ylmethoxy)benz-
5 aldoximinoyl chloride (738 mg, 2.00 mmol), methyl 4-
pentenoate (230 mg, 2.02 mmol) and TEA (0.28 mL, 2.0
mmol) were heated at reflux for 1 hour according to
Example 1, Part E. Crystallization from ether/hexanes
afforded 537 mg (60%). mp: 97.9-99.9 °C; ¹H NMR (300
10 MHz, CDCl₃) δ 7.57 (d, J = 9.0 Hz, 2H), 6.87 (d, J = 9.0
Hz, 2H), 4.74 (m, 1H), 4.15 (bd, J = 13.2 Hz, 2H), 3.81
(d, J = 6.2 Hz, 2H), 3.67 (s, 3H), 3.40 (dd, J = 16.5,
10.2 Hz, 1H), 2.95 (dd, J = 16.5, 7.3 Hz, 1H), 2.73 (dt,
J = 13.2, 1.1 Hz, 2H), 2.52 (t, J = 7.3 Hz, 2H), 1.98
15 (q, J = 7.0 Hz, 2H, overlapping m, 1H), 1.81 (bd, J =
12.8 Hz, 2H), 1.45 (s, 9H), 1.26 (dq, J = 12.4, 3.7 Hz,
2H).

Part G. 3-[3-[4-(N-t-Butyloxycarbonylpiperidin-4-ylmeth-
oxy)phenyl]- (5R,S)-isoxazolin-5-yl]propionic Acid

Methyl 3-[3-[4-(N-t-butyloxycarbonylpiperidin-4-
ylmethoxy)phenyl]- (5R,S)-isoxazolin-5-yl]propionate (250
mg, 0.560 mmol) was saponified using 0.5M LiOH (2 mL, 1
mmol) in THF (2 mL). The reaction was stirred at room
temperature for 3 hours, according to Example 1, Part F.
The resulting solid was crystallized from DCM/hexanes to
give 163 mg (67%) of the carboxylic acid; mp: 146.5-
147.7 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.57 (d, J = 8.8 Hz,
2H), 6.88 (d, J = 8.8 Hz, 2H), 4.75 (m, 1H), 3.81 (d, J
= 6.2 Hz, 2H), 3.41 (dd, J = 16.5, 10.3 Hz, 1H), 2.95
(dd, J = 16.5, 7.3 Hz, 1H), 2.75 (bt, J = 12.4 Hz, 2H),
2.57 (t, J = 7.3 Hz, 2H), 1.97 (m, 3H), 1.81 (bd, J =
12.1 Hz, 2H), 1.45 (s, 9H), 1.24 (m, 2H).

-131-

Part H. 3-[3-[4-(Piperidin-4-ylmethoxy)phenyl]- (5R,S)-isoxazolin-5-yl]propionic Acid, Trifluoroacetic Acid Salt

5 3-[3-[4-(N-t-Butyloxycarbonylpiperidin-4-ylmethoxy)phenyl]- (5R,S)-isoxazolin-5-yl]propionic acid (103 mg, 0.238 mmol) was Boc-deprotected using 33% TFA/DCM according to Example 1, Part G, giving 88 mg (83%) of the TFA salt; mp: 179.1-181.8 °C; ¹H NMR (400 MHz, MeOH-d₄) δ 7.60 (d, J = 9.0 Hz, 2H), 6.97 (d, J = 9.0 Hz, 2H), 4.73 (m, 1H), 3.94 (d, J = 6.1 Hz, 2H), 3.46 (m, 3H), 3.06 (m, 3H), 2.45 (dt, J = 7.3, 1.2 Hz, 2H), 2.16 (m, 1H), 2.08 (bd, J = 15.4 Hz, 2H); 1.94 (q, J = 6.6 Hz, 1H), 1.64 (dq, J = 14.2, 4.2 Hz, 2H).

15

Example 7

3-[4-(Piperidin-4-ylmethoxy)phenyl]- (5R,S)-isoxazolin-5-ylacetic Acid, Trifluoroacetic Acid Salt

20 Part A. Methyl 3-[4-(N-t-Butyloxycarbonylpiperidin-4-ylmethoxy)phenyl]- (5R,S)-isoxazolin-5-ylacetate

25 4-(N-t-Butyloxycarbonylpiperidin-4-ylmethoxy)benzaldoximoyl chloride (412 mg, 1.12 mmol), methyl 3-butenoate (200 mg, 2.00 mmol) and TEA (0.18 mL, 1.3 mmol) were heated at reflux for 2 hours according to Example 1, Part E. Crystallization from chloroform/cyclohexane afforded 329 mg (68%). mp: 97.9-99.9 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.58 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 5.04 (m, 1H), 4.15 (bd, J = 13.2 Hz, 2H), 3.81 (d, J = 6.2 Hz, 2H), 3.71 (s, 3H), 3.54 (dd, J = 16.8, 10.3 Hz, 1H), 3.08 (dd, J = 16.8, 7.3 Hz, 1H), 2.86 (dd, J = 16.1, 5.9 Hz, 1H), 2.73 (dt, J = 12.8, 1.8 Hz, 2H), 2.62 (dd, J = 15.8, 7.7 Hz, 1H),

-132-

1.95 (m, 1H), 1.81 (bd, $J = 13.2$ Hz, 2H), 1.45 (s, 9H),
1.25 (dq, $J = 12.8, 4.4$ Hz, 2H).

Part B. 3-[4-(N-t-Butyloxycarbonylpiperidin-4-ylmethoxy)phenyl]-(5R,S)-isoxazolin-5-ylacetic Acid

Methyl 3-[4-(N-t-butylloxycarbonylpiperidin-4-ylmethoxy)phenyl]-
10 (5R,S)-isoxazolin-5-ylacetate (329 mg, 0.762 mmol) was saponified using 0.5M LiOH (3 mL, 1.5 mmol) in THF (5 mL). The reaction was stirred at reflux for 4 hours, according to Example 1, Part F to give 72 mg (22%) of the carboxylic acid; mp: 164.0-164.8 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.58 (d, $J = 8.8$ Hz, 2H), 6.88 (d, $J = 8.8$ Hz, 2H), 5.07 (m, 1H), 4.15 (bd, $J = 13.6$ Hz, 2H), 3.82 (d, $J = 6.2$ Hz, 2H), 3.53 (dd, $J = 16.8, 10.3$ Hz, 1H), 3.10 (dd, $J = 16.8, 7.0$ Hz, 1H), 2.91 (dd, $J = 16.1, 5.9$ Hz, 1H), 2.73 (dt, $J = 14.6, 1.8$ Hz, 2H), 2.68 (dd, $J = 16.1, 7.3$ Hz, 1H), 1.97 (m, 1H), 1.81 (bd, $J = 13.2$ Hz, 2H), 1.45 (s, 9H), 1.26 (dq, $J = 12.8, 4.4$ Hz, 2H).

Part C. 3-[4-(Piperidin-4-ylmethoxy)phenyl]-(5R,S)-isoxazolin-5-ylacetic Acid. Trifluoroacetic Acid Salt

25 3-[4-(N-t-Butyloxycarbonylpiperidin-4-ylmethoxy)phenyl]-
0.172 mmol) was Boc-deprotected using 33% TFA/DCM according to Example 1, Part G, giving 64 mg (94%) of the TFA salt; mp: 220 °C (dec); ¹H NMR (300 MHz, MeOH-
30 d₄) δ 7.61 (d, $J = 9.2$ Hz, 2H), 6.97 (d, $J = 9.2$ Hz, 2H), 5.04 (m, 1H), 3.95 (d, $J = 5.9$ Hz, 2H), 3.56 (dd, $J = 17.2, 10.2$ Hz, 1H), 3.45 (bd, $J = 12.8$ Hz, 2H), 3.18 (dd, $J = 17.2, 7.3$ Hz, 1H), 3.04 (dt, $J = 10.2, 2.9$ Hz, 2H), 2.69 (m, 2H), 2.18 (m, 1H), 2.08 (bd, $J = 14.6$ Hz, 2H) 1.63 (bq, 2H).

-133-

Example 83-[4-(2-Piperidin-4-yl)ethoxyphenyl]-[5R, S]-isoxazolin-5-viropionic Acid, Trifluoroacetic Acid Salt

5 This material was prepared analogously to Example 1, giving the desired material; mp: 114.8-115.7 °C; ¹H NMR (300 MHz, CD₃OD) δ 7.59 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.4 Hz, 2H), 4.72 (m, 1H), 4.07 (t, J = 5.9 Hz, 2H), 3.47 (dd, J = 16.8, 10.2 Hz, 1H), 3.37 (dd, J = 16.8, 7.7 Hz, 1H), 2.98 (m, 2H), 2.44 (t, J = 7.3 Hz, 2H), 2.01 (bd, J = 15.0 Hz, 2H), 1.93 (m, 3H), 1.80 (m, 2H), 1.44 (m, 2H).

Example 915 erythro- and threo-3-[3-[4-[(piperidin-4-yl)methoxy]phenyl]isoxazolin-5-yl]butanesulfonylaminolpropionate, Trifluoroacetic Acid Salt

20 Part A. Dicyclohexylammonium D,L-2-[Butanesulfonyl]-aminol-4-pentenoic acid

To a suspension of D,L-2-amino-4-pentenoic acid (2.54 g, 22.06 mmol) in acetonitrile (35 mL) was added 25 BSTFA (7.3 mL, 27.5 mmol). The suspension was heated at 55 °C for 2 hours, after which time a golden yellow solution resulted. To this solution was added pyridine (2.2 mL, 27.2 mmol) and *n*-butanesulfonyl chloride (3.0 mL, 23.1 mmol). The mixture was heated at 70 °C for 20 hours, then cooled to room temperature. Concentration in vacuo afforded a brown oil, to which was added 15% KHSO₄ (5 mL). The mixture was stirred for 1 hour and shaken with EtOAc (3x). The combined organic extracts were washed with sat. NaCl, dried (MgSO₄), concentrated 35 and the resulting oil dissolved in ether (5 mL). To

-134-

this solution was added DCHA (4.38 mL, 22.0 mmol), causing immediate precipitation of the dicyclohexylammonium salt. The solid was collected by filtration and pumped to constant weight, giving 8.42 g (92%); mp: 5 207.1-208.6 °C; ¹H NMR (400 MHz, MeOH-d₄) δ 5.84 (m, 1H), 5.09 (dm, J = 17.1 Hz, 1H), 5.04 (dm, J = 10.2 Hz, 1H), 3.80 (dd, J = 7.1, 5.1 Hz, 1H), 3.18 (m, 2H), 3.02 (m, 2H), 2.49 (m, 2H), 2.06 (m, 4H), 1.78 (m, 8H), 1.55 (m, 12H), 0.94 (t, J = 7.3 Hz).

10

Part B. Methyl D,L-2-[(Butanesulfonyl)aminol]-4-pentenoate

To a solution of dicyclohexylammonium D,L-2-[(butanesulfonyl)aminol]-4-pentenoate (8.36 g, 20.07 mmol) in MeOH (50 mL) was added HCl-saturated MeOH (50 mL). The resulting suspension was stirred at room temperature for 18 hours, diluted with ether, and filtered. Concentration of the filtrate in vacuo was followed by the addition of ether, a second filtration, and washing of the filtrate with 0.1M HCl, sat. NaHCO₃, sat. NaCl. The solution was dried over anhydrous MgSO₄, concentrated and placed under vacuum until constant weight to give 4.49 g (90%) of the desired ester as a light brown oil; ¹H NMR (300 MHz, CDCl₃) δ 5.68 (m, 1H), 5.19 (bd, J = 1.5 Hz, 1H), 5.15 (m, 1H), 4.78 (bd, J = 8.4 Hz, 1H), 4.20 (dt, J = 8.8, 5.8 Hz, 1H), 3.77 (s, 3H), 2.99 (m, 2H), 2.54 (t, J = 6.6 Hz, 2H), 1.76 (m, 2H), 1.42 (sextuplet, J = 7.3 Hz, 2H), 0.93 (t, J = 7.3 Hz, 3H).

30

Part C. Methyl erythro- and threo-3-(3-14-[(Butyloxycarbonylpiperidin-4-yl)methoxy]phenyl)isoxazolin-5-yl[(butanesulfonylaminol)propionate

35

To a solution of 4-[(N-t-butyloxycarbonylpiperidin-4-yl)methoxy]benzaldoxime (2.680 g, 8.01 mmol),

-135-

methyl D,L-2-[(butanesulfonyl)amino]-4-pentenoate (2.000 g, 8.02 mmol) and TEA (0.11 mL, 0.79 mmol) in THF (10 mL) was added a 5% solution of NaOCl (common household bleach, 15 mL, 10.5 mmol). The resulting mixture was 5 rapidly stirred at room temperature for 20 hours. The mixture was diluted with EtOAc and water and the layers were separated. The aqueous portion was washed with EtOAc, and the combined organic fraction washed with sat. NaCl and dried over MgSO₄. Concentration in vacuo 10 afforded a light brown oil (4.8 g), which was purified using flash chromatography (0-50% EtOAc/hexanes in 5 steps), giving four components. The least polar of these materials (fractions 8-11) was determined by ¹H NMR to be the starting olefin (1.520 g, 76%). The next 15 component isolated in order of increasing polarity (fractions 12-15) was determined by ¹H NMR to be the starting oxime (1.423 g, 53%). The next component off of the column (fraction 20) was determined to be the faster of the two diastereomers (317 mg). This material 20 had co-eluted with an impurity having a ¹H NMR profile similar to the starting oxime and appeared to be approximately 50% pure. The most polar component isolated (fractions 22-25) was assigned as the second diastereomer (395 mg, 8%); mp: 127.5-129.3 °C; ¹H NMR 25 (300 MHz, CDCl₃) δ 7.56 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 5.25 (d, J = 9.5 Hz, 1H), 4.87 (m, 1H), 4.35 (dt, J = 9.2, 3.7 Hz, 1H), 4.15 (bs, 2H), 3.81, (d, J = 6.2 Hz, 2H), 3.78 (s, 3H), 3.49 (dd, J = 16.5, 10.3 Hz, 1H), 3.05 (t, J = 7.7 Hz, 2H), 2.97 (dd, J = 16.5, 30 7.0 Hz, 1H), 2.73 (bt, J = 12.1 Hz, 2H), 2.21 (m, 1H), 1.94 (m, 2H), 1.82 (m, 4H), 1.45 (s, 9H), 1.24 (m, 3H), 0.92 (t, J = 7.3 Hz, 3H).

Part D. 3-(3-[4-[(Butyloxycarbonylpiperidin-4-yl)methoxy]phenyl]isoxazolin-5-yl)[(butanesulfonylaminol)-propionic Acid (More Polar Diastereomer)]

A solution of methyl 3-(3-[4-[(butyloxycarbonylpiperidin-4-yl)methoxy]phenyl]isoxazolin-5-yl{[butanesulfonyl]amino})propionate more polar diastereomer (200 mg, 0.344 mmol) in THF (1 mL) was saponified using 0.5M LiOH (1 mL, 0.5 mmol) over 4 hours as per Example 1, Part F. The crude carboxylic acid was crystallized from EtOAc/hexanes, affording 77 mg (39%) of the desired material; mp: 137.3-139.0 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.55 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 5.45 (d, J = 9.5 Hz, 1H), 4.92 (m, 1H), 4.37 (m, 1H), 4.15 (b, 2H), 3.81, (d, J = 6.2 Hz, 2H), 3.47 (dd, J = 16.5, 9.9 Hz, 1H), 3.08 (t, J = 8.1 Hz, 2H), 3.01 (dd, J = 16.5, 7.0 Hz, 1H), 2.74 (bt, J = 12.1 Hz, 2H), 2.26 (m, 1H), 2.01 (m, 2H), 1.81 (m, 4H), 1.45 (s, 9H, overlapped with m, 1H), 1.24 (m, 3H), 0.91 (t, J = 7.3 Hz, 3H).

Part D'. 3-(3-[4-[(Butyloxycarbonylpiperidin-4-yl)methoxy]phenyl]isoxazolin-5-yl{[butanesulfonyl]amino})-20, propionic Acid (Less Polar Diastereomer)

A solution of the impure methyl 3-(3-[4-[(butyloxycarbonylpiperidin-4-yl)methoxy]phenyl]isoxazolin-5-yl{[butanesulfonyl]amino})propionate less polar diastereomer (309 mg) in THF (5 mL) was saponified using 0.5M LiOH (2 mL, 1 mmol) over 6 hours as per Example 1, Part F. The crude carboxylic acid was purified using flash chromatography (CHCl₃ - 5-15% MeOH/CHCl₃ step gradient) followed by crystallization from EtOAc/hexanes, affording 169 mg of the desired material; mp: 155 °C (dec); ¹H NMR (400 MHz, DMSO-d₆, 80 °C) δ 7.56 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 4.80 (m, 1H), 3.96 (bd, J = 13.2 Hz, 2H), 3.90 (d, J = 6.3 Hz, 2H), 3.77 (bs, 3H), 3.52 (t, J = 7.8 Hz, 1H), 3.38 (dd, J = 14.4, 10.0 Hz, 1H), 2.98 (t, J = 7.8 Hz, 2H), 2.76 (dt, J = 12.2, 1.7 Hz, 2H), 1.95 (m, 2H), 1.75 (m, 4H),

-137-

1.41 (s, 9H), 1.38 (d, J = 7.6 Hz, 1H), 1.25 (m, 4H),
0.88 (t, J = 7.3 Hz, 3H).

Part E. 3-[3-[4-[(Piperidin-4-yl)methoxy]phenyl]isoxazolin-5-yl]([butanesulfonyl]aminol)propionic Acid.
5 Trifluoroacetic Acid Salt (More Polar Diastereomer)

10 3-[(3-[4-[(Butyloxycarbonylpiperidin-4-yl)methoxy]phenyl]isoxazolin-5-yl)[butanesulfonyl]amino])propionic acid more polar diastereomer (40 mg, 0.070 mmol) was Boc-deprotected using 33% TFA/DCM according to Example 1, Part G. Recrystallization from methanol then afforded 4 mg (10%) of the TFA salt; mp: 263.5 °C (dec).

15 Part E'. 3-[3-[4-[(Piperidin-4-yl)methoxy]phenyl]isoxazolin-5-yl]([butanesulfonyl]aminol)propionic Acid.
Trifluoroacetic Acid Salt (Less Polar Diastereomer)

20 3-[(3-[4-[(Butyloxycarbonylpiperidin-4-yl)methoxy]phenyl]isoxazolin-5-yl)[butanesulfonyl]amino])propionic acid less polar diastereomer (98 mg, 0.173 mmol) was Boc-deprotected using 33% TFA/DCM according to Example 1, Part G, giving 40 mg of the TFA salt. Recrystallization from methanol then afforded 28 mg 25 (29%) of the pure amino acid; mp: 239.4-240.7 °C.

Example 33

30 4-Carboxymethyl-3-[4-(2-piperidin-4-yl)ethoxyphenyl-(5R,S)-isoxazolin-5-yl]acetic Acid. Trifluoroacetic Acid Salt

This material was prepared analogously to Example 1, giving the desired material; mp: 141.4 °C (dec); ¹H NMR (400 MHz, CD₃OD, 60 °C) δ 7.60 (d, J = 8.8 Hz, 2H), 35 6.96 (d, J = 8.8 Hz, 2H), 3.84 (d, J = 17.3 Hz, 1H), 3.66 (s, 3H), 3.59 (d, J = 17.3 Hz, 1H), 3.38 (bd, J =

-138-

12.9 Hz, 1H), 3.24 (t, J = 1.7 Hz, 2H), 3.21 (dm, J = 20.3 Hz, 1H), 3.04 (d, J = 1.5 Hz, 2H), 3.00 (dt, J = 12.9, 2.9 Hz, 2H), 2.02 (bd, J = 14.4 Hz, 2H), 1.95 (m, 1H), 1.81 (m, 2H), 1.48 (m, 2H).

5

Example 433(R,S)-{5(R,S)-N-[3-(4-Aminophenyl)isoxazolin-5-ylacetyl]amino}-3-phenylpropanoic Acid10 Part A. 4-Cyanobenzaldoxime

This material was prepared from 4-cyanobenzaldehyde according to Kawase and Kikugawa (J. Chem. Soc., Perkin Trans I 1979, 643).

15

Part B. Methyl 3-(3-Butenoyl)amino-3-phenylpropionate

To a solution of vinylacetic acid (861 mg, 10.0 mmol), methyl 3-amino-3-phenylpropionate hydrochloride 20 (2.37 g, 11.0 mmol) and TEA (1.6 mL, 12 mmol) in DCM (20 mL) at -10 °C was added DEC (2.11 g, 11.0 mmol). The resulting mixture was stirred at -10 °C for 15 hours. The mixture was then washed with water, 0.1 M HCl, sat. NaHCO₃, sat. NaCl and dried over anhydrous MgSO₄.

25 Concentration in vacuo followed by pumping until constant weight was achieved gave 2.36 g (95%) of the desired amide as a golden oil of suitable purity for further reaction; ¹H NMR (300 MHz, CDCl₃) δ 7.28 (m, 5H), 6.78 (bd, J = 7.7 Hz, 1H), 5.95 (m, 1H), 5.43 (dt, J = 8.4, 5.9 Hz, 1H), 5.25 (m, 2H), 3.61 (s, 3H), 3.04 (d, J = 7.0 Hz, 2H), 2.88 (dq, J = 15.0, 5.9 Hz, 2H).

-139-

Part C. Methyl 3(R,S)-(5(R,S)-N-[3-(4-Cyanophenyl)isoxazolin-5-ylacetyl]amino)-3-phenylpropanoate

This material was prepared from methyl 3-(3-
5 Butenoyl)amino-3-phenylpropionate (816 mg, 3.30 mmol)
and 4-cyanobenzaldoxime (438 mg, 3.00 mmol) according to
Example 4, Part B. The crude product was then purified
using flash chromatography (70% EtOAc/hexanes),
affording 731 mg (62%) of the desired isoxazolines as a
10 1:1 mixture of diastereomers; ^1H NMR (300 MHz, CDCl_3) δ
7.74 (m, 8H), 7.29 (m, 10H), 6.92 (bm, 2H), 5.42 (m,
2H), 5.16 (m, 2H), 3.64 (s, 3H), 3.60 (s, 3H), 3.48 (m,
2H), 3.26 (dd, $J = 17.3, 7.7$ Hz, 1H), 3.15 (dd, $J =$
16.8, 8.1 Hz, 1H), 2.85 (m, 2H), 2.69 (m, 2H).

15

Part D. Methyl 3(R,S)-(5(R,S)-N-[3-(4-Amidinophenyl)isoxazolin-5-ylacetyl]amino)-3-phenylpropanoate

20 Into a solution of methyl 3(R,S)-(5(R,S)-N-[3-(4-cyanophenyl)isoxazolin-5-ylacetyl]amino)-3-phenylpropanoate (587 mg, 1.50 mmol) in 10% DCM/methanol (55 mL) was bubbled dry HCl gas for 2 hours. The mixture was stirred for 18 hours, then concentrated *in vacuo*. The crude imidate was dissolved in methanol (20 mL) and ammonium carbonate added. The resulting mixture was stirred for 18 hours, then filtered. The filtrate was concentrated *in vacuo* and the residue purified using flash chromatography ($\text{CHCl}_3 - 20\%$ methanol/ CHCl_3). Concentration of the appropriate fractions *in vacuo* followed by placing the residue under vacuum until constant weight was achieved afforded 193 mg (32%) of the desired amidines; Mass Spectrum ($\text{NH}_3\text{-DCI}$, e/z , relative abundance) 409 ($\text{M} + \text{H})^+$, 100%.

-140-

Part E. 3(R,S)-{5(R,S)-N-[3-(4-Amidinophenyl)isoxazolin-5-ylacetyl]amino}-3-phenylpropanoic Acid, Trifluoroacetic Acid Salt

5. Methyl 3(R,S)-{5(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-3-phenylpropanoate (45 mg, 0.113 mmol) was saponified using 0.5 M LiOH (0.6 mL, 0.3 mmol) according to Example 1, Part F, affording 28 mg (49%); Mass Spectrum (NH₃-DCI, e/z, relative abundance) 412 (M¹⁰ + H)⁺, 100%.

Example 120a

Methyl 3(R)-{5(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-3-phenethylpropanoate

15

Part A. (E)-Methyl-5-phenyl-2-pentenoate

A solution of hydrocinnamaldehyde (13.42 g, 0.1 mol) and methyl(triphenylphosphoranylidene)acetate 20 (33.44 g, 0.1 mol) in THF was stirred at reflux for 20 hours. The reaction mixture was concentrated under vacuum and the residue was purified by flash chromatography using hexane:EtOAc::9:1. The desired product was obtained as a clear, pale yellow oil (8.0 g, 0.042 mol, 42%); ¹H NMR (300 MHz, CDCl₃) δ 7.3-7.2 (m, 2H), 7.2-7.1 (m, 3H), 7.1-6.9 (m, 1H), 5.85 (d, 1H, J = 5.8 Hz), 3.75 (s, 3H), 2.8 (t, 2H, J = 7.7 Hz), 2.55 (q, 2H, J = 7.4 Hz); MS (NH₃-DCI) 191 (M+H)⁺.

30. Part B. Methyl 3-(R)-[N-(1-(R)-1-phenylethyl)aminol-5-phenylpentanoate

A mixture of (E)-methyl-5-phenyl-2-pentenoate (5.70 g, 0.03 mol) and R-methylbenzylamine (14.54 g, 0.12 mol) 35 was heated at 110°C over 94 hours. The cooled reaction mixture was purified by flash chromatography using

-141-

hexane:EtOAc::8:2 to afford 1.18 g (0.0038 mol, 12%) of the desired product as a clear liquid; ^1H NMR (300 MHz, CDCl_3) δ 7.4-7.0 (m, 11H), 3.9 (q, 1H, J = 6.5 Hz), 3.65 (s, 3H), 2.9-2.65 (m, 2H), 2.6-2.35 (m, 3H), 1.75-1.6 (m, 2H), 1.35 (d, 3H, J = 6.2 Hz); MS (NH₃-DCI) 312 (M+H)⁺.

Part C. Methyl 3-(R)-amino-5-phenylpentanoate • acetic acid salt

10

A mixture of methyl 3-(R)-[N-(1-(R)-1-phenylethyl)amino]-5-phenylpentanoate (0.72 g, 2.3 mmol), 20% $\text{Pd}(\text{OH})_2/\text{C}$ (0.38 g), cyclohexene (8.2 mL), glacial HOAc (0.13 mL, 2.3 mmol), and MeOH (15 mL) was heated at reflux under N_2 for 20 hours. After cooling, the catalyst was removed by filtration through a Celite plug, rinsed with MeOH, and the solution concentrated under vacuum. The residue was triturated with hexane to afford 0.46 g (96%) of a white solid, mp = 73-75°C; ^1H NMR (300 MHz, DMSO) δ 8.3 (bs, 2H), 7.35-7.15 (m, 5H), 3.65 (s, 3H), 3.45-3.35 (m, 1H), 2.8-2.6 (m, 4H), 2.0-1.7 (m, 2H); $[\alpha]_D^{25} -12.50^\circ$ (c=0.0032, MeOH).

Part D. Methyl 3(R)-(5(R,S)-N-[3-(4-cyanophenyl)isoxazolin-5-ylacetyl]amino)heptanoate

To a suspension of 3-(4-cyanophenyl)isoxazolin-5-ylacetic acid (460 mg, 2.0 mmol) in EtOAc (15 ml) was added methyl 3-(R)-amino-5-phenylpentanoate acetic acid salt (410 mg, 2.0 mmol), TBTU (640 mg, 2.0 mmol), and Et₃N (0.56 mL, 400 mg, 4.0 mmol). After stirring at room temp for 16 hours, the reaction mixture was concentrated under vacuum then purified by flash chromatography using EtOAc to afford 690 mg (83%) of a colorless oil. ^1H NMR (300 MHz, DMSO) δ 8.05 (brs, 1H), 7.95-7.9 (m, 2H), 7.85-7.8 (m, 2H), 7.3-7.25 (m, 2H),

-142-

7.2-7.1 (m, 2H), 5.15-5.0 (m, 1H), 4.15-4.0 (m, 1H), 3.6 (d, 3H, $J = 9.9$ Hz), 3.3 (d, 2H, $J = 6.9$ Hz), 3.25-3.15 (m, 1H), 2.75-2.35 (m, 6H), 1.8-1.6 (m, 2H); MS (NH₃-DCI) 420 (M+H)⁺.

5

Part E Methyl 3(R)-[5(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino]-3-phenethylpropanoate

10 This material was prepared from methyl 3(R)-[5(R,S)-N-[3-(4-cyanophenyl)isoxazolin-5-ylacetyl]amino]-3-phenethylpropanoate (670 mg, 1.6 mmol) according to Example 43, Part D. The crude product was triturated with cold ether to afford 272 mg (39%) of a 15 white solid of the title compound as a 1:1 mixture of diastereomers, mp = 76-78°C; ¹H NMR (300 MHz, DMSO) δ 8.1-8.0 (m, 1H), 8.0-7.8 (m, 4H), 7.95-7.85 (m, 5H), 7.35-7.2 (m, 5H), 5.1-5.0 (m, 1H), 4.1-4.0 (m, 1H), 3.6 (s, 3H), 3.3-3.15 (m, 2H), 2.7-2.4 (m, 6H), 1.8-1.7 (m, 2H), 1.1-1.0 (m, 2H); Mass Spectrum (NH₃-ESI,) 437 (M + H)⁺.

Example 120b

25 Methyl 3(S)-[5(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino]-3-phenethylpropanoate

Part A. Methyl 3-(S)-[N-(1-(R)-1-phenylethyl)amino]-5-phenylpentanoate

30 A mixture of (E)-methyl-5-phenyl-2-pentenoate (5.70 g, 0.03 mol) and R-methylbenzylamine (14.54 g, 0.12 mol) was heated at 110°C over 94 hours. The cooled reaction mixture was purified by flash chromatography using hexane:EtOAc::8:2 to afford 1.20 g (0.0039 mol, 13%) of 35 the desired product as a clear liquid; ¹H NMR (300 MHz, CDCl₃) δ 7.35-7.0 (m, 11H), 3.9 (q, 1H, $J = 6.6$ Hz),

-143-

3.65 (s, 3H), 2.95-2.8 (m, 1H), 2.75-2.5 (m, 2H), 2.45-
2.35 (m, 2H), 1.9-1.65 (m, 2H), 1.3 (d, 3H, $J = 6.6$ Hz);
MS (NH₃-DCI) 312 (M+H)⁺.

5 Part B. Methyl 3-(S)-amino-5-phenylpentanoate • acetic acid salt

Methyl 3-(S)-[N-benzyl-N-(1-(R)-1-phenylethyl)amino]heptanoate (0.93 g, 2.9 mmol), 20%
10 Pd(OH)₂/C (0.47 g), cyclohexene (10.1 mL), glacial HOAc (0.17 mL, 2.9 mmol), and MeOH (20 mL) were heated at reflux under N₂ for 48 hours. After cooling, the catalyst was removed by filtration through a Celite plug, rinsed with MeOH, and the solution concentrated
15 under vacuum. The residue was triturated with hexane to afford 0.65 g (80%) of a white solid, mp = 86-88°C; ¹H NMR (300 MHz, CDCl₃) δ 7.35-7.15 (m, 5H), 5.3 (brs, 2H), 3.65 (s, 3H), 3.35-3.2 (m, 1H), 2.8-2.55 (m, 3H), 2.5-2.4 (m, 1H), 2.0 (s, 3H), 1.8 (q, 2H, $J = 7.4$ Hz);
20 $[\alpha]_D^{25} +9.55^\circ$ (c=0.220, MeOH).

Part C. Methyl 3-(S)-(R,S)-N-[3-(4-cyanophenyl)isoxazolin-5-ylacetyl]amino]heptanoate

25 To a suspension of 3-(4-cyanophenyl)isoxazolin-5-ylacetic acid (700 mg, 2.6 mmol) in EtOAc (15 ml) was added methyl 3-(S)-amino-5-phenylpentanoate acetic acid salt (600 mg, 2.6 mmol), TBTU (830 mg, 2.6 mmol), and Et₃N (1.09 mL, 790 mg, 7.8 mmol). After stirring at room temp 16 hours, the reaction mixture was concentrated under vacuum then purified by flash chromatography using EtOAc to afford 420 mg (38%) of a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 8.05-8.0 (m, 1H), 7.95-7.9 (m, 2H), 7.85-7.8 (m, 2H), 7.3-7.2 (m, 2H), 7.2-7.1 (m, 3H), 5.15-5.0 (m, 1H), 4.15-4.0 (m,

-144-

1H), 3.6-3.55 (m, 3H), 3.3-3.1 (m, 1H), 2.7-2.4. (m, 6H), 1.8-1.6 (m, 2H); MS (NH₃-DCI) 420 (M+H)⁺.

Part D. Methyl 3(S)-[5(R,S)-N-[3-(4-
5 amidinophenyl)isoxazolin-5-ylacetyl]amino]-3-
phenethylpropanoate

This material was prepared from methyl 3(S)-
(5(R,S)-N-[3-(4-cyanophenyl)isoxazolin-5-
10 ylacetyl]amino)-3-phenethylpropanoate (360 mg, 0.86
mmol) according to Example 43, Part D. The crude
product was triturated with cold ether to afford 230 mg
(62%) of an amorphous solid of the title compound as a
1:1 mixture of diastereomers, mp = 84-86°C; ¹H NMR (300
15 MHz, DMSO) δ 8.1-8.0 (m, 1H), 8.0-7.8 (m, 4H), 7.75-7.7
(m, 1H), 7.3-7.1 (m, 6H), 5.1-5.0 (m, 1H), 4.15-4.0 (m,
1H), 3.65 (s, 3H), 3.3-3.1 (m, 1H), 2.7-2.6 (m, 3H),
2.5-2.4 (m, 3H), 1.8-1.65 (m, 2H), 1.1-1.0 (m, 2H);
Mass Spectrum (NH₃-ESI) 437 (M + H)⁺.

20

Example 189

5(R,S)-(2-Piperidin-4-yl)ethyl-8-(2-carboxyethyl)-1-oxa-
2,8-diazaspiro[4.4]non-2-ene-7,9-dione

25

Part A. 3-(N-t-Butyloxycarbonylpiperidin-4-yl)propanal

To a suspension of PCC (11.52 g, 53.44 mmol) and
sodium acetate (4.38 g, 53.4 mmol) in DCM (60 mL) was
30 added a solution of 3-(N-t-butyloxycarbonylpiperidin-4-
yl)propanol (10.00 g, 41.09 mmol) in DCM (20 mL). After
4 hours at room temperature, the mixture was diluted
with ether and passed though a short column of
fluorisil® using ether as an eluent. The eluate was
35 concentrated in vacuo and placed under vacuum until
constant weight was achieved, affording 8.32 g (84%) of

-145-

the desired aldehyde as a colorless oil; ^1H NMR (300 MHz, CDCl_3) δ 9.76 (t, J = 1.5 Hz, 1H), 4.05 (bs, 2H), 2.64 (bt, J = 11.7 Hz, 2H), 2.45 (dt, J = 7.3, 1.5 Hz, 2H), 1.60 (m, 3H), 1.43 (s, 9H, overlapped with m, 2H), 1.08 (dq, J = 12.1, 4.0 Hz, 2H).

5 Part B. (E,Z)-3-(N-t-Butyloxycarbonylpiperidin-4-yl)propanal Oxime

10 To a solution of 3-(N-t-butyloxycarbonylpiperidin-4-yl)propanal (3.905 g, 16.18 mmol) in EtOH : pyr = 1 : 1 (20 mL) was added hydroxylamine hydrochloride (1.701 g, 24.48 mmol) and the resulting solution stirred at room temperature for 20 hours. Concentration in vacuo, 15 resulted in an oil, which was dissolved in EtOAc and washed with 0.1 M HCl (3x), water, sat. CuSO_4 (2x), water and brine. The solution was dried over MgSO_4 , concentrated in vacuo and placed under vacuum until constant weight was achieved, affording 4.071 g (98%) of 20 a 1 : 1 mixture of the (E,Z)-oxime as a colorless oil; ^1H NMR (300 MHz, CDCl_3) δ 7.42 (t, J = 6.2 Hz, 0.5H), 6.70 (t, J = 5.5 Hz, 0.5H), 4.06 (bs, 2H), 2.67 (bt, J = 12.8 Hz, 2H), 2.41 (m, 1H), 2.23 (m, 1H), 1.66 (b, 2H), 1.45 (s, 9H, overlapped with m, 4H), 1.08 (m, 2H).

25 Part C. Methyl (5R,S)-3-[12-(N-t-Butyloxycarbonylpiperidin-4-yl)ethyl]-5-carboxymethylisoxazolin-5-yl acetate

To a solution of (E,Z)-3-(N-t-butyloxycarbonylpiperidin-4-yl)propanal oxime (503 mg, 1.96 mmol) and 30 dimethyl itaconate (620 mg, 3.92 mmol) in DCM (3 mL) was added a 5% solution of sodium hypochlorite (common household bleach, 3 mL, 2 mmol). The resulting mixture was stirred overnight (19 hours) at room temperature. 35 The layers were separated and the aqueous washed with DCM (2x). The combined DCM fraction was dried over

-146-

$MgSO_4$ and concentrated *in vacuo*. Purification using flash chromatography (hexanes - 10% EtOAc/hexanes - 50% EtOAc/hexanes) followed by concentration and pumping to constant weight afforded the desired isoxazoline (510 mg, 63%) as a colorless oil; 1H NMR (300 MHz, $CDCl_3$) δ 4.06 (bd, $J = 13.6$ Hz, 2H), 3.78 (s, 3H), 3.67 (s, 3H), 3.57 (d, $J = 17.6$ Hz, 1H), 3.15 (d, $J = 16.5$ Hz), 3.06 (d, $J = 17.6$ Hz, 1H), 2.86 (d, $J = 16.5$ Hz, 1H), 2.65 (bt, $J = 12.1$ Hz, 2H), 2.36 (m, 2H), 1.65 (m, 2H, 10 overlapped with H_2O , 2H), 1.43 (s, 9H), 1.07 (m, 2H).

Part D. (5R,S)-3-[(2-(N-t-Butyloxycarbonylpiperidin-4-yl)ethyl]-5-carboxyisoxazolin-5-yl]acetic Acid

15 To a solution of methyl (5R,S)-3-[(2-(N-t-butyloxycarbonylpiperidin-4-yl)ethyl]-5-carboxymethylisoxazolin-5-yl)acetate (380 mg, 0.921 mmol) was saponified using 0.5M LiOH (5 mL, 2.5 mmol) in THF (5 mL). The reaction was stirred at ambient temperature for 5 hours, 20 according to Example 1, Part F to give 240 mg (68%) of the diacid; mp: 154.4-154.9 °C; 1H NMR (300 MHz, $MeOH-d_4$) δ 4.04 (bd, $J = 13.2$ Hz, 2H), 3.52 (d, $J = 17.8$ Hz, 1H), 3.18 (d, $J = 17.8$ Hz, 1H), 2.97 (AB quartet, $\Delta = 32.6$, $J = 16.8$ Hz, 2H), 2.72 (b, 2H), 2.39 (m, 2H), 1.71 (bd, $J = 13.2$ Hz, 2H), 1.51 (m, 3H), 1.43 (s, 9H), 1.05 (m, 2H).

Part E. 5(R,S)-2-(N-t-Butyloxycarbonylpiperidin-4-yl)ethyl-8-[(2-(1,1-dimethylethoxycarbonyl)ethyl]-1-oxa-30 2,8-diazaspiro[4.4]non-2-ene-7,9-dione

To a solution of (5R,S)-3-[(2-(N-t-butyloxycarbonylpiperidin-4-yl)ethyl]-5-carboxyisoxazolin-5-yl)acetic acid (700 mg, 1.82 mmol) in THF (5 mL) was added DCC (378 mg, 1.83 mmol), and the resulting suspension was stirred for 30 min at room temperature. To this mixture

-147-

was added a suspension of β -alanine *t*-butyl ester hydrochloride (372 mg, 2.05 mmol) and TEA (300 μ L, 2.15 mmol) in THF (5 mL). The mixture was stirred overnight (18 hours) at room temperature. Following dilution with 5 EtOAc, the mixture was filtered and the filtrate washed with 0.1M HCl, sat. NaHCO₃ and sat. NaCl. It was dried over anhydrous MgSO₄, concentrated and placed under vacuum until constant weight was reached, giving 430 mg (46%) of the crude amide. A portion of this material 10 (420 mg, 0.821 mmol) was dissolved in THF (4 mL). To this solution was added HOSuc (100 mg, 0.869 mmol) followed by DCC (180 mg, 0.872 mmol). The resulting suspension was stirred at room temperature for 18 hours. Following dilution with ether, the mixture was cooled to 15 0 °C and filtered. The filtrate was dried over anhydrous MgSO₄, concentrated and placed under vacuum until constant weight was reached, giving 430 mg (86%) of the crude active ester. A portion of this material (402 mg, 0.660 mmol) was dissolved in DMF (5 mL) at 0 20 °C. To this solution was added NaH (16 mg, 0.66 mmol). After 3 hours at 0 °C, the reaction was quenched with HOAc. After dilution with EtOAc, the mixture was washed with water (4x), sat. NaHCO₃, water, 0.1M HCl and sat. NaCl. It was dried over anhydrous MgSO₄, concentrated 25 and placed under vacuum until constant weight was reached, giving 230 mg (70%) of the crude imide. The crude material was purified using flash chromatography (CHCl₃ - 5% MeOH/CHCl₃), affording 149 mg (46%) of a colorless oil after concentration of the appropriate fractions and pumping to constant weight; ¹H NMR (300 MHz, CDCl₃) δ 4.09 (b, 2H), 3.82 (t, J = 7.3 Hz, 2H), 3.54 (d, J = 17.2 Hz, 1H), 3.12 (d, J = 18.7 Hz, 1H), 2.98 (d, J = 17.2 Hz, 1H), 2.83 (d, J = 18.7 Hz, 1H), 2.69 (m, 2H), 2.57 (t, J = 7.3 Hz, 2H), 2.42 (m, 2H), 30 1.68 (m, 2H), 1.57 (m, 2H), 1.45 (s, 9H, coincident with m, 1H), 1.11 (m, 2H).

-148-

Part F. 5(R,S)-(2-Piperidin-4-yl)ethyl-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]non-2-ene-7,9-dione

5

To a solution of 5(R,S)-2-(N-t-butyloxycarbon-yl)piperidin-4-yl)ethyl-8-[(2-(1,1-dimethylethoxycarbon-yl)ethyl]-1-oxa-2,8-diazaspiro[4.4]non-2-ene-7,9-dione (75 mg, 0.152 mmol) in DCM (1 mL) was added TFA (0.5 mL, 10 8 mmol). The reaction was stirred at room temperature for 2 hours, then was concentrated *in vacuo*. Excess TFA was chased by rotary evaporation with toluene (2x).

Crystallization from MeOH/ether gave 10 mg (15%) of the desired amino acid after pumping to constant weight; mp:

15 178.0-179.1 °C; ¹H NMR (400 MHz, DMSO-d₆, 60 °C) δ 12.15 (bs, 1H), 8.26 (bs, 2H), 3.64 (m, 2H), 3.39 (d, J = 17.8 Hz, 1H), 3.26 (m, 3H), 2.98 (AB quartet, Δ = 71.3 Hz, J = 18.3 Hz, 2H), 2.85 (m, 2H), 2.50 (m, 1H, coincident with DMSO-d₅), 2.37 (t, J = 7.6 Hz, 2H), 1.84 (bd, J = 11.7 Hz, 2H), 1.58 (m, 1H), 1.52 (t, J = 7.6 Hz, 2H), 1.29 (m, 2H).

Example 190

5(R,S)-(2-Piperidin-4-yl)ethyl-8-(3-carboxypropyl)-1-oxa-2,8-diazaspiro[4.4]non-2-ene-7,9-dione

This material was prepared using the procedures outlined in Example 189, giving the title compound; mp: 133.4-135.1 °C; ¹H NMR (400 MHz, CD₃OD, 55 °C) δ 3.59 (t, J = 6.8 Hz, 2H), 3.50 (d, J = 17.7 Hz, 1H), 3.38 (bd, J = 12.9 Hz, 2H), 3.18 (d, J = 17.7 Hz, 1H), 2.98 (m, 4H), 2.85 (m, 2H), 2.50 (m, 1H, coincident with DMSO-d₅), 2.45 (m, 2H), 2.31 (t, J = 7.1 Hz, 2H), 2.00 (m, 2H), 1.98 (pentuplet, J = 7.1 Hz, 2H), 1.40 (m, 2H).

-149-

Example 275

N³-[3-(4-amidinophenyl)isoxazolin-5(R, S)-ylacetyl-L-2,3-diaminopropionic acid TEA salt5 Part A. 3-(4-cyanophenyl)isoxazolin-5(R, S)-ylacetic acid.

To a solution of 4-cyanobenzaldoxime (see Ex 43, Part A) (312 g, 2.13 mol) in tetrahydrofuran (3000 ml) at room temperature was added vinyl acetic acid (552g, 6.41 mol). The yellow solution was cooled in an ice bath and sodium hypochlorite solution (5200 ml) was added in a dropwise fashion over 2h. After stirring overnight at room temperature the reaction was quenched with a 5% citric acid solution and diluted with 200ml ether. The layers were separated and the aqueous acidified to pH 4 using citric acid. The acid layer was washed twice with 200 ml ether, the ether layers combined and extracted with saturated sodium bicarbonate solution. After acidifying the basic layer with citric acid, the product was extracted into 400 ml ether. The organic phase was washed three times with 150 ml water, once with brine, dried ($MgSO_4$) and concentrated to give 220g of 3-(4-cyanophenyl)isoxazolin-5-ylacetic acid as a white solid. Recrystallization from 25% water/ethanol yielded 165g of analytically pure material. Anal. Calcd for $C_{12}H_{10}N_2O_3$: C, 62.61; H, 4.38; N, 12.17. Found: C, 62.37; H 4.47; N, 11.71. 1H NMR (300MHz, $CDCl_3$): δ 7.77-7.76 (d, 2H, $J=1.8Hz$); 7.72-7.71 (d, 2H, $J=1.8Hz$); 5.22-5.14 (m, 1H); 3.63-3.54 (dd, 1H, $J=10.6Hz$, 16.8Hz); 3.19-3.11 (dd, 1H, $J=7.3Hz$, 16.8Hz); 3.00-2.93 (dd, 1H, $J=6.2Hz$, 16.5Hz); 2.79-2.72 (dd, 1H, $J=7.3Hz$, 16.5Hz). IR (KBr pellet): 3202, 2244, 1736, 1610, 1432, 1416, 1194, 1152, 928, 840, 562 cm^{-1} .

35 Part B. Methyl N²-Cbz-L-2,3-diaminopropionate HCl salt.

-150-

5 N^2 -Cbz-L-2,3-diaminopropionic acid (10 mmol, 2.39 g) was dissolved in 20 mL methanol and 20 mL 4 N HCl in dioxane and the solution was stirred for 4 hours and then concentrated to give a solid. The solid was washed with ether several times to give 2.50 g (87%) product.

10 NMR (DMSO-d₆): δ 8.38 (b, 3H); 7.96 (d, 1H); 7.38 (m, 5H); 5.05 (s, 2H); 4.44 (m, 1H); 3.66 (s, 3H); 3.14 (m, 2H).

15 **Part C. Methyl N^2 -Cbz- N^3 -[3-(4-cyanophenyl)isoxazolin-5(R, S)-ylacetyl]-L-2,3-diaminopropionate.**

20 To a solution of 3-(4-cyanophenyl)isoxazolin-5(R, S)-ylacetic acid (19 mmol, 4.37 g), methyl N^2 -Cbz-L-2,3-diaminopropionate HCl salt (20 mmol, 5.76 g) and triethylamine (60 mmol, 8.36 mL) was added TBTU (20 mmol, 6.42 g) and the solution was stirred for 2 hours. Ethyl acetate was added and the solution was washed with dilute citric acid, brine, NaHCO₃ and brine, dried (MgSO₄), and concentrated. Crystallization from ethyl acetate/ether gave 6.85 g (78%) product. NMR (DMSO-d₆): δ 8.16 (t, 1H); 7.92 (d, 2H); 7.82 (d, 2H); 7.68 (d, 1H); 7.36 (m, 5H); 5.04 (m, 3H); 4.20 (m, 1H); 3.64 (s, 3H); 3.50 (m, 2H); 3.26 (m, 2H); 2.50 (m, 2H).

25 **Part D. Methyl N^3 -[3-(4-amidinophenyl)isoxazolin-5(R, S)-ylacetyl]-L-2,3-diaminopropionate HCl salt.**

30 HCl gas was bubbled into a solution of methyl N^2 -Cbz- N^3 -[3-(4-cyanophenyl)isoxazolin-5(R, S)-ylacetyl]-L-2,3-diaminopropionate (2.1 mmol, 1.0 g) for 1 hour and the solution was stirred overnight and concentrated. The residue was dissolved in 30 mL 2 M ammonia in methanol and the solution was stirred overnight, and concentrated to give 1.2 g crude product.

-151-

E. Methyl N³-[3-(4-amidinophenyl)isoxazolin-5(R, S)-ylacetyl]-L-2,3-diaminopropionic acid TFA salt.

5 Methyl N³-[3-(4-amidinophenyl)isoxazolin-5(R, S)-ylacetyl]-L-2,3-diaminopropionate HCl salt (200 mg) was saponified with 1 mL methanol and 1 mL 1 N NaOH for 1 hour, and acidified with acetic acid. Purification on reversed phase HPLC gave 40 mg product. ESI (M+H)⁺: Calcd 334.2; Found 334.2.

10

Example 276

N²-Cbz-N³-[3-(4-amidinophenyl)isoxazolin-5(R, S)-ylacetyl]-L-2,3-diaminopropionic acid TFA salt

15

Part A. Methyl N²-Cbz-N³-[3-(4-amidinophenyl)isoxazolin-5(R, S)-ylacetyl]-L-2,3-diaminopropionate TFA salt.

20

To a solution of the compound of Ex. 275, part E (1.0 mmol, 385 mg) and sodium bicarbonate (5.0 mmol, 400 mg) in 2 mL water, 2 mL acetonitrile and 1 mL DMF was added benzyl chloroformate (1 mmol, 143 μ L) and the mixture was stirred for 2 hours at room temperature. The solution was filtered, acidified with TFA and purified on reversed phase HPLC to give 150 mg (25%) product. NMR (DMSO-d₆): δ 9.40 (s, 2H); 9.20 (s, 2H); 8.18 (t, 1H); 7.86 (m, 4H); 7.68 (d, 1H); 7.35 (m, 5H); 5.02 (m, 3H); 4.20 (m, 1H); 3.64 (s, 3H); 3.52 (m, 2H); 3.26 (m, 2H); 2.50 (m, 2H).

30

Part B. N²-Cbz-N³-[3-(4-amidinophenyl)isoxazolin-5(R, S)-ylacetyl]-L-2,3-diaminopropionic acid TFA salt.

35

Methyl N²-Cbz-N³-[3-(4-amidinophenyl)isoxazolin-5(R, S)-ylacetyl]-L-2,3-diaminopropionate TFA salt (0.12 mmol, 70 mg) was dissolved in 2 mL methanol and 1 mL 1 N NaOH and after 1 hour, the solution was acidified

-152-

with acetic acid. Purification on reversed phase HPLC gave 50 mg (74%) product. ESI (M+H)⁺: Calcd 468.2; Found 468.2.

5

Example 278

N²-n-butyloxycarbonyl-N³-[3-(4-amidinophenyl)isoxazolin-5(R, S)-ylacetyl]-L-2,3-diaminopropionic acid TFA salt

10 Part A. Methyl N²-n-butyloxycarbonyl-N³-[3-(4-amidinophenyl)isoxazolin-5(R, S)-ylacetyl]-L-2,3-diaminopropionate TFA salt.

15 To a solution of the compound of Ex. 275, part E (1.0 mmol, 385 mg) and sodium bicarbonate (2.5 mmol, 200 mg) in 2 mL water, 2 mL acetonitrile and 1 mL DMF cooled in an ice bath was added n-butyl chloroformate (1 mmol, 127 μ L). After stirring for 1 hour, the solution was acidified with acetic acid and purified on reversed phase HPLC to give 150 mg (27%) product. NMR (DMSO-d₆):

20 δ 9.40 (s, 2H); 9.20 (s, 2H); 8.16 (t, 1H); 7.86 (m, 4H); 7.47 (d, 1H); 5.02 (m, 1H); 4.16 (m, 1H); 3.94 (t, 2H); 3.62 (s, 3H); 3.50 (m, 2H); 3.26 (m, 2H); 2.50 (m, 2H); 1.52 (m, 2H); 1.32 (m, 2H); 0.88 (t, 3H). ESI (M+H)⁺: Calcd 448.3; Found 448.3.

25

Part B. N²-n-butyloxycarbonyl-N³-[3-(4-amidinophenyl)isoxazolin-5(R, S)-ylacetyl]-S-2,3-diaminopropionic acid TFA salt.

30

Methyl N²-n-butyloxycarbonyl-N³-[3-(4-amidinophenyl)isoxazolin-5(R, S)-ylacetyl]-S-2,3-diaminopropionate TFA salt (0.107 mmol, 60 mg) was dissolved in 2 mL methanol and 2 mL 1 N NaOH and after 1 hour, the solution was acidified with acetic acid.

35

Purification on reversed phase HPLC gave 53 mg (89%) product. ESI (M+H)⁺: Calcd 434.3; Found 434.3.

-153-

Example 314A

Methyl N²-n-butyloxycarbonyl-N³-(3-(4-
amidinophenyl)isoxazolin-5(S)-ylacetyl)-(S)-2,3-
diaminopropionate TFA salt

5

Part A: Methyl N²-Cbz-N³-Boc-L-2,3-diaminopropionate.

To a solution of methyl N²-Cbz-(S)-2,3-diaminopropionate HCl salt (16.3 mmol, 4.7 g) and di-10 tert-butyl dicarbonate (16.3 mmol, 3.56 g) in 30 mL chloroform cooled in an ice bath was added triethylamine (34 mmol, 4.7 mL) and the solution was stirred in the ice bath for 1 hour and at room temperature for 3 hours and concentrated. The residue was taken up in ethyl 15 acetate and the solution was washed with dilute citric acid, brine, NaHCO₃ and brine, dried (MgSO₄), and concentrated. Crystallization from ether/petroleum ether gave 5.2 g (92%) product. NMR (DMSO-d₆): δ 7.60 (d, 1H); 7.35 (m, 5H); 6.88 (t, 1H); 5.02 (s, 2H); 4.14 (m, 1H); 20 3.60 (s, 3H); 3.28 (m, 2H); 1.37 (s, 9H).

Part B: Methyl N³-Boc-(S)-2,3-diaminopropionate HCO₂H salt. A mixture of methyl N²-Cbz-N³-Boc-(S)-2,3-diaminopropionate (14 mmol, 5.0 g), formic acid (42 mmol, 1.6 mL) and 10% Pd/C (500 mg) in 40 mL methanol 25 was stirred at room temperature for 1 hour and filtered through a celite. The filtrate was concentrated and the residue was triturated with ether-petroleum ether to give 3.7 g (100%) solid product. NMR (DMSO-d₆): δ 8.20 (s, 1H); 6.90 (t, 1H); 5.36 (b, 3H); 3.61 (s, 3H); 3.51 (t, 1H); 3.18 (t, 2H); 1.38 (s, 9H).

Part C: Methyl N²-n-butyloxycarbonyl-N³-Boc-(S)-2,3-diaminopropionate.

35

To a mixture of methyl N³-Boc-(S)-2,3-diaminopropionate HCO₂H salt (14 mmol, 3.7 g) and NaHCO₃

-154-

(40 mmol, 3.4 g) in 10 mL water and 10 mL THF cooled in an ice bath was added slowly butyl chloroformate (16 mmol, 2 mL) over 15 min. After stirring for 1 hour, ethyl acetate was added and the solution was washed with 5 dilute citric acid, brine, NaHCO_3 and brine, dried (MgSO_4), and concentrated to give 4.4 g (100%) oily product. NMR (DMSO-d₆): δ 7.37 (d, 1H); 6.84 (t, 1H); 4.10 (m, 1H); 3.96 (t, 2H); 3.60 (s, 3H); 3.26 (m, 2H); 1.52 (m, 2H); 1.38 (s, 9H); 1.36 (m, 2H); 0.88 (t, 3H).

10

Part D: Methyl N²-butyloxycarbonyl-(S)-2,3-diaminopropionate TFA salt.

Methyl N²-n-butyloxycarbonyl-N³-BOC-(S)-2,3-diaminopropionate (13.9 mmol, 4.4 g) was dissolved in 25 mL methylene chloride and 35 mL TFA and after 1 hour, the solution was concentrated to give an oily product. Yield 4.8 g (100%). NMR (DMSO-d₆): δ 8.02 (b, 3H); 7.68 (d, 2H); 4.38 (m, 1H); 3.99 (t, 2H); 3.68 (s, 3H); 3.22 (m, 1H); 3.06 (m, 1H); 1.55 (m, 2H); 1.34 (m, 2H); 0.89 (t, 3H).

Part E: Methyl-N²-n-butyloxycarbonyl-N³-(3-(4-cyanophenyl)isoxazolin-5(S)-ylacetyl)-(S)-2,3-diaminopropionate

To a solution of 3-(4-cyanophenyl)isoxazolin-5(S)-ylacetic acid (5.2 mmol, 1.2 g). [Chiral starting material was prepared from the racemic compound of Ex. 275, Part A by resolution on a 50 X 2 cm Chiralpak AD column using 0.1% TFA/EtOH at 10° C to give isomer A (faster eluting) and isomer B (slower eluting). Alternately, the isomers were resolved by crystallization of the chinconidine salt of the 5-S isomer of the isoxazolines from acetone, leaving the 5(R) isomer in the mother liquor. The absolute

-155-

stereochemistry of the crystalline salt was determined by X-ray crystallography to be the 5(S) isoxazoline.] and methyl-N²-butyloxycarbonyl-(S)-2,3-diaminopropionate TFA salt (6 mmol, 1.53 g) in 20 ml DMF cooled in an ice bath was added diisopropylethylamine (20 mmol, 3.5 mL) followed by BOP (5.5 mmol, 2.43 g). After stirring at room temperature for 3 hours, ethyl acetate was added and the solution was washed with 0.5 N HCl, brine, NaHCO₃ and brine, dried (MgSO₄), and concentrated to give 1.9 g (87%) product. NMR (DMSO-d₆): δ 8.12 (t, 1H); 7.94 (d, 2H); 7.83 (d, 2H); 7.46 (d, 1H); 5.04 (m, 1H); 4.16 (m, 1H); 3.96 (t, 2H); 3.64 (s, 3H); 3.58 (dd, 1H); 3.40 (m, 2H); 3.20 (dd, 1H); 2.56 (dd, 1H); 2.43 (dd, 1H); 1.52 (m, 2H); 1.32 (m, 2H); 0.88 (t, 3H).

15

Part F: Methyl-N²-n-butyloxycarbonyl-N³-[3-(4-aminophenyl)isoxazolin-5(S)-ylacetyl-(S)-2,3-diaminopropionate TFA salt.

20 To a solution of methyl-N²-n-butyloxycarbonyl-N³-[3-(4-cyanophenyl)isoxazolin-5(S)-ylacetyl]-(S)-2,3-diaminopropionate (4.4 mmol, 1.9 g) in 50 mL methanol was bubbled with HCl gas at 0°C for 1 hour and the solution was stirred at room temperature for 5 hours and concentrated. The residue was taken up in 20 mL methanol and ammonium carbonate (11 mmol, 1.1 g) was added. The mixture was stirred at room temperature overnight and concentrated. The solid was dissolved in methanol/water/TFA and purification on reversed phase HPLC gave 1.0 g (40%) product. ESI (M+H)⁺: Calcd 448.3; Found 448.3.

25

30

Example 314B

35 Methyl-N²-n-butyloxycarbonyl-N³-[3-(4-aminophenyl)isoxazolin-5(R)-ylacetyl-(S)-2,3-diaminopropionate TFA salt

-156-

Part A: 3-(4-cyanophenyl)-5(R)-ylacetic acid

This material was resolved from 3-(4-cyanophenyl)isoxazolin-5(R,S)-ylacetic acid as described above in the procedure for Example 314A, Part E.

Part B: Methyl-N²-n-butyloxycarbonyl-N³-[3-(4-cyanophenyl)isoxazolin-5(R)-ylacetyl]-S-2,3-diaminopropionate

10 10 diaminopropionate.

This material was synthesized from 3-(4-cyanophenyl)-5(R)-ylacetic acid (4.3 mmol, 1.0 g), Methyl-N²-butyloxycarbonyl-(S)-2,3-diaminopropionate TFA

15 salt (5 mmol, 1.27 g), BOP (4.5 mmol, 2 g) and diisopropylethylamine (16 mmol, 2.8 mL) using the same procedure as for XVI. Yield 1.75 g (95%). NMR (DMSO-d₆): δ 8.12 (t, 1H); 7.94 (d, 2H); 7.83 (d, 2H); 7.46 (d, 1H); 5.04 (m, 1H); 4.16 (m, 1H); 3.96 (t, 2H); 3.64 (s, 2H); 3.58 (dd, 1H); 3.40 (m, 2H); 3.20 (dd, 1H); 2.56 (dd, 1H); 2.43 (dd, 1H); 1.52 (m, 2H); 1.32 (m, 2H); 0.88 (t, 3H).

Part C: Methyl-N²-n-butyloxycarbonyl-N³-[3-(4-amidinophenyl)isoxazolin-5(R)-ylacetyl]-S-2,3-diaminopropionate TFA salt

This compound was synthesized from Methyl-N²-n-butyloxycarbonyl-N³-[3-(4-cyanophenyl)isoxazolin-5(R)-ylacetyl]-S-2,3-diaminopropionate (4.0 mmol, 1.7 g) using the same procedure as for Example 314A, Part G. Yield 1.0 g (45%). ESI (M+H)⁺: Calcd 448.3; Found 448.3.

Example 344

35 Methyl 3(R)-{5(R,S)-N-[3-(4-Amidinophenyl)isoxazolin-5-ylacetyl]amino}heptanoate.

Part A. (E)-Methyl 2-heptenoate

To a solution of diethyl methylphosphonoacetate (19
5 ml, 104 mmol) in dry THF (800 ml) at -4 °C was added 64
ml of n-BuLi (1.6 M in hexane, 102 mmol) dropwise over
45 min. The resulting solution was stirred 1 h at room
temp. Valeraldehyde (10.0 ml, 94 mmol) was added and
stirred 3.5 h at room temp. The reaction was quenched
10 with 25 ml sat. NH₄Cl. Solvents were distilled at
atmospheric pressure, and the resulting solids were
taken up in EtOAc, extracted with water and brine, and
dried with Na₂SO₄. The solvents were again distilled at
atmospheric pressure, and the resulting yellow liquid
15 was distilled under house vacuum to yield 7.2 g clear
liquid, boiling range under house vacuum 90-125 °C;
HRMS, e/z Calc. for (M+H)⁺: 143.1072. Found:
143.1070; IR(film) 1728, 1658 cm⁻¹.

20 Part B. N-(1-(R)-1-Phenylethyl)benzamide

A solution of benzoyl chloride (22.5 mL, 0.19 mole)
in dichloromethane (10 mL) was added dropwise over 1.5 h
to a 0 °C solution of (R)-(+)- α -methylbenzylamine (25
25 mL, 0.19 mole), triethylamine (31 mL, 0.22 mole), and 4-
DMAP (100 mg), in dichloromethane (1 L). After 1.75 h
at 0 °C the mixture was concentrated *in vacuo*, then
diluted with EtOAc. This mixture was extracted with
water, 1 M HCl, water, and brine, then dried (MgSO₄)
30 and concentrated to yield 43.4 g of a colorless
crystalline solid; mp 121.0-121.5 °C; IR(KBr) 3332,
1636 cm⁻¹; [α]_D²⁵ -2.30° (c=1.002, CH₂Cl₂); Anal.
Calc. for C₁₅H₁₅NO: C, 79.97; H, 6.71; N, 6.22.
Found: C, 79.88; H, 6.65; N, 6.17.

Part C. N-(1-(R)-1-Phenylethyl)-N-benzylamine

BH₃/THF (1 M in THF, 220 mL, 220 mmol) was added dropwise over 1 h to a 0 °C solution of the above 5 benzamide (20 g, 89 mmol) in dry THF (200 mL). The ice bath was removed, and the mixture was heated to reflux for 40 h. A TLC analysis indicated incomplete reaction, so more BH₃/THF (1 M in THF, 30 mL, 30 mmol) was added, and heating resumed for 22.5 h. After cooling, MeOH 10 (250 mL) was added dropwise cautiously over 5 h. The resulting mixture was boiled for 2 h, then cooled and concentrated in vacuo. Reconcentration from MeOH (2 x 500 mL) and drying under high vacuum gave 19.3 g of an oil containing a small amount of a precipitate. This 15 crude product was stirred with hot 2 M HCl (140 mL) to generate a clear solution, then slowly cooled to RT, and ultimately in an ice bath to yield a crystalline solid, as described by Simpkins (Tetrahedron 1990, 46(2), 523). The solid was collected by filtration and rinsed with a 20 small amount of water. After air drying for 3 d, 16.35 g of the hydrochloride salt was obtained; mp 178.5-179.5 °C; [α]_D²¹ +18.9° (c=4.0, EtOH). The salt was converted to the free base by extraction with Et₂O and aq. KOH, then Kugelrohr distilled, oven temp. 120-140 °C 25 (1.1 mm Hg) to give 12.5 g of an oil; [α]_D²¹ +61.2° (c=3.98, EtOH); Anal. Calc. for C₁₅H₁₇N: C, 85.26; H, 8.11; N, 6.63. Found: C, 84.93; H, 7.75; N, 6.58.

30 Part D. Methyl 3-(R)-[N-benzyl-N-(1-(R)-1-phenylethyl)aminolheptanoate

Following the asymmetric Michael addition method of Davies (Tetrahedron:Asymmetry 1991, 2(3), 183), n-35 butyllithium (1.6 M in hexanes, 4.4 mL, 7.0 mmol) was

-159-

added dropwise over 3 min to a 0 °C solution of *N*-(1-(*R*)-1-phenylethyl)-*N*-benzylamine (1.5 g, 7.0 mmol) in dry THF (35 mL). After 30 min, the resulting dark pinkish-red solution was cooled to -78 °C, and a 5 solution of methyl 2-heptenoate (0.50 g, 3.5 mmol) in THF (10 mL) was added dropwise over 10 min. After 13 min, the cold reaction was quenched with saturated NH₄Cl (7 mL). After warming to RT, the mixture was extracted with Et₂O and brine, dried (MgSO₄), and concentrated in 10 vacuo. The product was purified by chromatography over silica gel, eluting with 0% to 50% EtOAc in hexane. The cleanest major product fractions (apart from a few mixed fractions) were concentrated in vacuo to give 0.91 g of a pale yellow oil which by NMR is a single diastereomer, 15 with the newly generated asymmetric center assigned as 3(*R*) by analogy with the Davies reference above; ¹³C NMR (300 MHz, CDCl₃) δ 173.31, 143.40, 141.78, 128.40, 128.27, 128.11, 128.00, 126.91, 126.67, 57.90, 54.22, 51.32, 50.05, 36.83, 33.28, 29.32, 22.72, 19.40, 14.12; 20 [α]_D²⁵ +12.96° (c=0.602, MeOH).

Part E. Methyl 3-(*R*)-aminoheptanoate • acetic acid salt

Methyl 3-(*R*)-[*N*-benzyl-*N*-(1-(*R*)-1-phenylethyl)amino]heptanoate (0.70 g, 2.0 mmol), 20% Pd(OH)₂/C (0.35 g), cyclohexene (7 mL), glacial HOAc (0.12 mL, 2.1 mmol), and MeOH (14 mL) were heated at reflux under N₂ for 20.5 h. After cooling, the catalyst was removed by filtration thru a Celite plug, rinsed 30 with MeOH, and the solution concentrated in vacuo. Drying overnight under high vacuum yielded 0.43 g of a viscous oil; ¹³C NMR (300 MHz, CDCl₃) δ 177.64, 171.52, 51.97, 48.22, 37.24, 33.08, 27.50, 23.31, 22.29, 13.76; [α]_D²⁵ -10.6° (c=0.602, MeOH).

-160-

Part F. Methyl 3(R)-{5(R,S)-N-[3-(4-cyanophenyl)isoxazolin-5-ylacetyl]amino}heptanoate

To a suspension of 3-(4-cyanophenyl)isoxazolin-5-ylacetic acid (300 mg, 1.3 mmol) in EtOAc (10 ml) was added methyl 3-(R)-aminohheptanoate acetic acid salt (287 mg, 1.3 mmol), TBTU (420 mg, 1.3 mmol), and Et₃N (600 μ l, 4.3 mmol). After stirring at room temp 2.5 h, the reaction mixture was extracted with 5% KHSO₄, sat 10 NaHCO₃, and brine, then dried with Na₂SO₄. Evaporation, followed by chromatography over silica gel in 50-100% EtOAc/hexanes yielded 245 mg colorless glass. MS (NH₃-DCI) Calc. for (M+H)⁺: 372, (M+NH₄)⁺: 389. Found: 372, 389.

15

Part G. Methyl 3(R)-{5(R,S)-N-[3-(4-Amidinophenyl)isoxazolin-5-ylacetyl]amino}heptanoate

To a solution of methyl 3(R)-{5(R,S)-N-[3-(4-cyanophenyl)isoxazolin-5-ylacetyl]amino}heptanoate (179 mg, .48 mmol) in 15 ml dry MeOH at 0 °C, was added a stream of HCl gas generated from dropping two 20 ml portions of H₂SO₄ into solid NaCl over 35 min. After stirring 20 h at room temp, the solvent was removed with 25 a rapid stream of N₂. Et₂O was added and removed with a rapid stream of N₂. The resulting gummy oil was taken up in 15 ml dry MeOH, to which was added (NH₄)₂CO₃ (1.1g, 11.4 mmol). After stirring 19.5 h at room temp, the solvent was removed with a rapid stream of N₂, and the 30 resulting white solid was purified by chromatography over silica gel, eluting with 0-20% MeOH/CHCl₃. Purified product was taken up in 5% MeOH/CHCl₃ and filtered. Concentration of the filtrate yielded 100 mg white solid. IR(KBr) 3600-2800, 1734, 1676, 1640 cm⁻¹;

-161-

HRMS, e/z Calc. for $(M+H)^+$: 389.2189. Found:
389.2192.

Example 348

5 Ethyl 3(R)-[5(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-
ylacetyl]amino]-5-methylhexanoate • trifluoroacetic acid
salt

Part A. (E)-Ethyl 5-methyl-2-hexenoate

10 Prepared in analogous fashion to methyl 2-heptenoate, using triethyl phosphonoacetate, stirring 17 h at room temp upon addition of isovaleraldehyde. Distillation under house vacuum yielded 72% clear oil, boiling range under house vacuum 80-130 °C; IR(film) 1724, 1656 cm^{-1} .

Part B. Ethyl 3-(R)-[N-benzyl-N-(1-(R)-1-phenylethyl)amino]-5-methylhexanoate

20 Prepared in analogous fashion via the asymmetric Michael addition of Ex. 344, part D above. Yield a viscous pale yellow oil (65%); ^{13}C NMR (300 MHz, CDCl_3) δ 172.83, 143.56, 142.17, 128.27, 128.21, 128.15, 25 128.03, 126.96, 126.60, 60.10, 58.56, 52.43, 50.09, 43.23, 36.72, 24.76, 23.48, 22.13, 20.20, 14.21; $[\alpha]_D^{25} +5.12^\circ$ ($c=0.606$, EtOH).

Part C. Ethyl 3-(R)-amino-5-methylhexanoate • acetic acid salt

30 Prepared as previously described except EtOH was used as solvent. Yield a waxy solid (94%); mp 57-61 °C; HRMS, e/z Calc. for $(M+H)^+$: 174.1494. Found:
35 174.1485.

-162-

Part D. Ethyl 3-(R)-amino-5-methylhexanoate •
hydrochloric acid salt

The above acetic acid salt (1.1 g, 4.7 mmol) was
5 stirred 4 min in 4 M HCl/dioxane (5.0 ml). The
resulting solution was triturated with Et₂O, cooled, and
the clear liquid decanted, leaving an orange oil which
solidified to 960 mg waxy solid on high vacuum; ¹H NMR
(300 MHz, CDCl₃) δ 8.49 (br, 3H), 4.20 (q, J = 7.3, 2H),
10 3.70-3.65 (m, 1H), 2.86-2.80 (m, 2H), 1.83-1.80 (m, 2H),
1.58-1.54 (m, 1H), 1.30-1.26 (t, J = 7.3, 3H), 0.99-0.91
(m, 6H).

Part E. Ethyl 3-(R)-[5(R,S)-N-[3-[4-(N-t-
15 butoxycarbonylamidino)phenyl]isoxazolin-5-
ylacetylamino]-5-methylhexanoate

To a suspension of 3-[4-(N-t-
butoxycarbonylamidino)phenyl]isoxazolin-5-ylacetic acid
20 (78 mg, 0.22 mmol) in EtOAc (5 ml) was added ethyl 3-
(R)-amino-5-methylhexanoate hydrochloride salt (47 mg,
0.22 mmol), TBTU (72 mg, 0.22 mmol), and Et₃N (100 μl,
0.72 mmol). After stirring 6 h at room temp, the
reaction mixture was extracted with pH 4 buffer
25 (potassium hydrogen phthalate), sat NaHCO₃, and brine,
then dried with Na₂SO₄. Evaporation, followed by
chromatography over silica gel in 100% EtOAc yielded 33
mg colorless glass; ¹H NMR (300 MHz, CDCl₃) δ 7.90 (d, J
= 8.4, 2H), 7.70 (dd, J = 8.5, J' = 1.9, 2H), 6.32-6.28
30 (m, 1H), 5.13-5.11 (m, 1H), 4.34-4.33 (m, 1H), 4.17-4.09
(m, 2H), 3.56-3.47 (m, 1H), 3.25-3.17 (m, 1H); 2.71-2.46
(m, 4H), 1.66-1.47 (m, 2H), 1.56 (s, 9H), 1.31-1.23 (m,
4H), 0.92 (dd, J = 6.6, J' = 1.8, 3H), 0.84 (d, J = 6.6,
3H).

-163-

Part F. Ethyl 3(R)-{5(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-5-methylhexanoate • trifluoroacetic acid salt

5 The product from Part E above (29 mg, 0.058 mmol) was dissolved in DCM (300 μ l), to which was added TFA (100 μ l). The resulting solution was stirred at room temp under a CaSO_4 drying tube for 3.5 h, and triturated with Et_2O . 24 mg white solid were collected by 10 filtration; ^1H NMR (300 MHz, CDCl_3) δ 9.4 (br, 1H), 9.0 (br, 1H), 7.8 (s, 4H), 5.0 (m, 1H), 4.2 (m, 1H), 4.0 (q, 2H), 3.6 (m, 1H), 3.3 (m, 2H), 2.4 (m, 3H), 1.6 (m, 1H), 1.4 (m, 1H), 1.2 (m, 4H), 0.8 (m, 6H); HRMS, e/z Calc. for $(\text{M}+\text{H})^+$: 403.2345. Found: 403.2363.

15

Example 350

20 Methyl 3(R,S)-{5(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-4-(phenylthio)butanoate • hydrochloric acid salt:

Part A. Methyl phenylthioacetoacetate

To a solution of thiophenol (5.00 ml, 48.6 mmol) in DMF (20 ml), K_2CO_3 (10.09 g, 73 mmol) and methyl 25 chloroacetoacetate (5.93ml, 48.6 mmol) were added. The reaction mixture was stirred 6 h at 50 °C, diluted with EtOAc , and extracted with saturated Na_2SO_4 , water, and brine, then dried (Na_2SO_4) and concentrated. The 30 resulting oil was chromatographed with 20% EtOAc in Hexane to yield 9.40 g yellow oil; MS (CH4-DCI) Calc. for $(\text{M}+\text{H})^+$: 224. Found: 224; IR (KBr) 2954, 1656, 1438, 626 cm^{-1} .

35 Part B. Methyl-3(R,S)-amino-4-phenylthiobutanoate

-164-

To a solution of methyl phenylthioacetoacetate (1.00 g, 4.5 mmol) in MeOH (20 ml), ammonium formate (4.26 g, 6.75 mmol) and sodium cyanoborohydride (0.42 g, 6.7 mmol) were added. The reaction mixture was stirred at room temperature for 18 h, then diluted with EtOAc and partitioned into 1 M HCl. The aqueous layer was then basified to pH = 8.0 with NaOH. The desired product was extracted out with EtOAc, washed with water and brine, dried over Na₂SO₄ and concentrated to yield 0.61 g yellow oil; MS (NH₃-CI/DDIP) Calc. for (M+H)⁺: 226. Found: 226; ¹H NMR (300 MHz, CDCl₃) δ 7.39 (d, J = 7, 2H); 7.32-7.26 (m, 3H), 7.22 (d, J = 10, 1H), 3.74 (s, 3H), 3.39-3.31 (m, 1H), 3.13-3.07 (dd, J = 13, J' = 9, 1H), 2.91-2.83 (dd, J = 12, J' = 6, 1H), 2.65-2.58 (dd, J = 12, J' = 6, 1H), 2.46-2.38 (dd, J = 16, J' = 8, 1H).

Part C. Methyl-3(R,S)-(5(R,S)-N-[3-(4-cyanophenyl)isoxazolin-5-yl]acetyl)amino)-4-(phenylthio)butanoate

To a suspension of 3-(4-cyanophenyl)isoxazolin-5-ylacetic acid (0.50 g, 2 mmol) in EtOAc (10 ml), methyl-3(R,S)amino-4-(phenylthio)butanoate (0.51 g, 2 mmol), TBTU (0.71 g, 2 mmol), and Et₃N (1.24 ml, 8.9 mmol) were added. The reaction mixture was stirred 2 h at room temperature, diluted with EtOAc, washed with 5% citric acid, saturated NaHCO₃, and brine, dried over Na₂SO₄, concentrated, and the resulting oil was chromatographed over silica gel in 100% EtOAc to yield 0.61 g of a yellow glass; MS (NH₃-CI/DDIP) Calc. for (M+H)⁺: 438.1. Found: 438; Anal. Calc. for C₃₂H₂₃N₃O₄S₁: C, 63.31; H, 5.30; N, .60; S, 7.33. Found: C, 62.99; H, 5.22; N, 9.53; S, 7.30.

-165-

Part D. Methyl 3(R,S)-{5(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyllamino]-4-(phenylthio)butanoate • hydrochloric acid salt

5 The product from Part C above (0.30 g, 0.68 mmol) was dissolved in dry MeOH (20 ml) at 0 °C. To the resulting solution, HCl gas was bubbled in from a generator as described in Example 344, Part G, over a period of 2 h. The generator was removed and the 10 reaction mixture stirred at 0 °C for 18 h, then concentrated and triturated with CHCl₃. The resulting precipitate was collected by filtration and redissolved in dry MeOH (20 ml). To this solution, ammonium carbonate (0.99 g, 10 mmol) was added and the mixture 15 stirred at room temperature for 18 h. The solution was concentrated and recrystallized from DCM/MeOH to yield 0.14 g white solid; HRMS, *e/z* Calc. for (M+H)⁺: 455.1753. Found: 455.175; ¹H NMR (300 MHz, *d*₆-DMSO) δ 9.44 (br s, 1H), 9.18 (br s, 1H), 8.22 (d, *J* = 10, 1H), 20 7.86 (m, 4H), 7.41-7.25 (m, 4H), 7.2 (m, 1H), 5.03 (m, 1H), 4.2 (m, 1H), 3.59 (s, 3H), 3.29-3.05 (m, 4H), 2.8-2.39 (m, 4H).

Example 359

25

Methyl 3(R,S)-{5(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyllamino]-4-(phenylsulfonamido)butanoate • trifluoroacetic acid salt;

30 Part A. Methyl 3-(R,S)-hydroxy-4-aminobutanoate • hydrochloric acid salt

Chlorotrimethylsilane (100 mL, 0.79 mol) was added dropwise over 1.5 h to a stirred 0 °C suspension of 4-35 amino-3-(R,S)-hydroxybutyric acid (25 g, 0.21 mol) in

-166-

MeOH (1 L). The resulting clear solution was allowed to slowly warm to room temperature overnight. The solvent was evaporated in vacuo, and the resulting residue was reconcentrated from more MeOH (2 x 500 mL). Drying under high vacuum produced 37 g of a viscous oil; ^{13}C NMR (300 MHz, d_6 -DMSO) δ 171.42, 90.14, 64.67, 51.89, 44.39; Anal. Calc. for $\text{C}_5\text{H}_{16}\text{ClNO}_3$: C, 35.41; H, 7.13; N, 8.26; Cl, 20.90. Found: C, 35.18; H, 7.09; N, 8.18; Cl, 20.77.

10

Part B. Methyl 3-(R,S)-hydroxy-4-(phenylsulfonamido)butanoate

A solution of benzenesulfonyl chloride (7.5 mL, 59 mmol) in dichloromethane (10 mL) was added dropwise over 55 min to a 0 °C solution of the Part A amine salt (10 g, 50 mmol), and Et₃N (17 mL, 120 mmol) in dichloromethane (110 mL). The mixture was allowed to slowly warm to room temperature, and stirring was continued over the weekend. After solvent removal in vacuo, the mixture was diluted with EtOAc and extracted with H₂O, 0.1 M HCl, and brine. Drying (MgSO₄) and solvent removal in vacuo yielded 14.6 g of a viscous oil; ^{13}C NMR (300 MHz, CDCl₃) δ 172.67, 139.79, 132.78, 129.22, 127.02, 66.77, 52.01, 47.72, 38.31; Anal. Calc. for C₁₁H₁₅NO₅S: C, 48.34; H, 5.53; N, 5.13; S, 11.73. Found: C, 48.44; H, 5.61; N, 4.90; S, 11.34.

20

Part C. Methyl 3-oxo-4-(phenylsulfonamido)butanoate

30

The Part B alcohol (2.8 g, 10 mmol) was oxidized with Jones reagent under standard conditions. The ketone was purified by chromatography on silica gel, eluting with 0% to 100% EtOAc in hexane, to yield 1.11 g of a waxy solid; mp 94.5-95.5 °C; ^{13}C NMR (300 MHz, CDCl₃) δ 197.08, 166.80, 139.17, 133.08, 129.29, 127.17,

-167-

52.71, 51.91, 46.15; Anal. Calc. for $C_{11}H_{13}NO_5S$: C, 48.70; H, 4.83; N, 5.16; S, 11.82. Found: C, 48.77; H, 4.69; N, 5.08; S, 11.88.

5 Part D. Methyl 3-(R,S)-3-amino-4-(phenylsulfonamido)butanoate

To a room temperature solution of the Part C ketone (0.71 g, 2.6 mmol) in MeOH (7 mL) and THF (3 mL) was 10 added ammonium formate (2.5 g, 39 mmol) and sodium cyanoborohydride (0.25 g, 3.9 mmol). After 45.5 h, solvent was evaporated, and the residue was diluted with EtOAc (70 mL). This solution was extracted with 1.0 M NaOH, H_2O , and brine. After concentration, the product 15 was purified by chromatography on silica gel, eluting with 0% to 100% EtOAc in hexane, then 1% to 20% MeOH in EtOAc to yield 0.16 g of a viscous oil, which eventually solidified; 1H NMR (300 MHz, $CDCl_3$) δ 9.79 (br, 2H), 7.84 (d, 2H, J = 8 Hz), 7.81 (br, 1H), 7.68-7.53 (m, 3H), 4.05-3.92 (m, 1H), 3.75 (s, 3H), 3.33-3.17 (m, 2H), 20 2.89-2.72 (m, 2H); HRMS, e/z Calc. for $(M+H)^+$: 273.0909. Found: 273.0916.

Part E. Methyl 3-(R,S)-(5(R,S)-N-[3-(4-(N-t-butoxycarbonylamido) phenyl)isoxazolin-5-ylacetyl]amino)-4-(phenylsulfonamido)butanoate

This compound was prepared analogous to Example 348, Part E, stirring 24 h in 5 ml EtOAc and 1 ml DMF. 30 Chromatography in 5% MeOH/ $CHCl_3$ yielded 80% of an orange solid; IR(KBr) 3296, 2338, 1736, 1660, 1618 cm^{-1} ; HRMS, e/z Calc. for $(M+H)^+$: 602.2285. Found: 602.2270.

-168-

Part F. Methyl 3(R,S)-{5(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-4-(phenylsulfonamido)butanoate · trifluoroacetic acid salt

5 The product from Part E was deprotected analogously to Example 348, Part F, yielding 86% pink solid; IR(KBr) 3312, 3104, 1734, 1670; HRMS, e/z Calc. for $(M+H)^+$: 502.1760. Found: 502.1761. The more active diastereomer (based on PRP assay) was isolated from the 10 above mixture by SFC HPLC, Chiralpak AD - 2X25 cm, eluted with 0.1% TFA/25% MeOH/75% CO₂. Under these conditions, the more active diastereomer eluted last.

Example 362

15

Methyl 3(R,S)-{5(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-4-(n-butylsulfonamido)butanoate · trifluoroacetic acid salt;

20 Part A. Methyl 3-(R,S)-hydroxy-4-(n-butylsulfonamido)butanoate

This compound was prepared entirely analogously to Ex.359, Part B, using *n*-butylsulfonylchloride instead. 25 A colorless, waxy solid of excellent purity was obtained in 65% yield without purification; mp 46-50 °C; ¹³C NMR (300 MHz, CDCl₃) δ 172.64, 67.29, 52.56, 51.99, 47.83, 38.40, 25.57, 21.52, 13.55; Anal. Calc. for C₉H₁₉NO₅S: C, 42.67; H, 7.56; N, 5.53; S, 12.66. 30 Found: C, 42.69; H, 7.59; N, 5.36; S, 12.78.

Part B. Methyl 3-oxo-4-(n-butylsulfonamido)butanoate

The immediately preceding alcohol was oxidized as 35 described for Example 359, Part C, to give a 57% yield

-169-

of a colorless solid; mp 53-55 °C; Anal. Calc. for C₉H₁₇NO₅S: C, 43.02; H, 6.82; N, 5.57; S, 12.76.
Found: C, 42.68; H, 7.03; N, 5.74; S, 13.06.

5 Part C. Methyl 3(R,S)-3-amino-4-(n-butylsulfonamido)butanoate

This compound was prepared analogous to Example 350, Part B, using the product from Part B above (1.20 g, 4.8 mmol) yielding 0.26 g yellow oil; ¹H NMR (300 MHz, CDCl₃) δ 3.70 (s, 3H), 3.38 (m, 1H), 3.24-3.13 (m, 1H), 3.02 (m, 4H), 2.58-2.52 (dd, J = 16, J' = 11, 1H), 1.79 (m, 2H), 1.24 (m, 2H), 0.95 (t, 3H); MS (NH₄-DCI) Calc. for (M+H)⁺: 271. Found: 271.

15

Part D. Methyl-3(R,S)-(5(R,S)-N-[3-(4-(N-t-butoxycarbonylamidine) phenyl]isoxazolin-5-ylacetyllamino)-4-(n-butylsulfonamido)butanoate

20 To a solution 3-[4-(N-t-butoxycarbonylamidine)phenyl]isoxazolin-5-ylacetic acid (0.24 g, 0.83 mmol) in DMF (20 ml), the product from Part C above (0.29 gr, 0.83 mmol), TBTU (0.27 g, 0.83 mmol), and Et₃N (0.46 ml, 3.3 mmol) was added. After 25 stirring 4 h at room temperature, the reaction mixture was diluted with EtOAc, extracted with pH 4 buffer (potassium hydrogen phthalate), saturated NaHCO₃, brine, then dried (NaSO₄). Concentration, followed by chromatography over silica gel in 100% EtOAc, yielded 1.17 g of a white foam; MS (NH₃-DCI) Calc. for (M+H)⁺: 582.3. Found: 582; IR(KBr) 3312, 2338, 1620, 1144 cm⁻¹.

30 Part E. Methyl 3(R,S)-(5(R,S)-N-[3-(4-amidinophenyl]isoxazolin-5-ylacetyllamino)-4-(n-butylsulfonamido)butanoate · trifluoroacetic acid

-170-

To a solution of the product from Part D above (0.22 g, 0.37 mmol) in DCM (10 ml), trifluoroacetic acid (2.2 ml) was added. The reaction mixture was stirred 2 h at room temperature, triturated with Et₂O, and the resulting precipitate was chromatographed over silica gel in 20% MeOH in CHCl₃ to yield 0.20 g white solid; HRMS, e/z Calc. for (M+H)⁺: 482.2073. Found: 482.2090; mp = 178-184 °C.

-171-

Example 365

Methyl (5(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetylamino]-4-(methoxycarbonyl)butanoate •

5 trifluoroacetic acid salt;

Part A. Dimethyl 3-aminoglutarate • hydrochloric acid salt

10 This product was prepared similarly to Example 359, Part A, from β -glutamic acid to yield the diester as a colorless gum in quantitative yield; HRMS, e/z Calc. for $(M+H)^+$: 176.0923. Found: 176.0933.

15 Part B. Methyl (5(R,S)-N-[3-(4-(N-t-butoxycarbonylamino)phenyl)isoxazolin-5-ylacetylamino]-4-(methoxycarbonyl)butanoate

Prepared analogous to Example 359, Part E, to yield 20 32% of a white solid; IR(KBr) 3306, 2338, 1738, 1656, 1620 cm^{-1} ; HRMS, e/z Calc. for $(M+H)^+$: 505.2298. Found: 505.2283.

Part C. Methyl (5(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetylamino]-4-(methoxycarbonyl)butanoate • trifluoroacetic acid salt

Prepared analogous to Example 348, Part F, yielding 25 83% white solid; IR(KBr) 3316, 3102, 2340, 1736, 1670 30 cm^{-1} ; HRMS, e/z Calc. for $(M+H)^+$: 405.1774. Found: 405.1775.

Example 368

-172-

Methyl 3(R,S)-{5(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyllamino]-4-(methoxycarbonyl)pentanoate • trifluoroacetic acid salt;

5 Part A. Dimethyl 3-(R,S)-amino adipate • hydrochloric acid salt

This product was prepared as in Example 359, Part A, from β -amino adipic acid to yield a colorless gum in 10 quantitative yield; HRMS, e/z Calc. for $(M+H)^+$: 190.1079. Found: 190.1080.

Part B. Methyl-3(R,S)-{5(R,S)-N-[3-(4-(N-t-butoxycarbonylamidine) phenyl]isoxazolin-5-ylacetyllamino]-4-(methoxycarbonyl) pentanoate

This product was prepared similarly as in Example 362, Part D, using the product from Part B above (0.70 g, 3.1 mmol) instead to yield 1.17 g of a white foam; 20 HRMS, e/z Calc. for $(M+H)^+$: 519.2454. Found: 519.2459; Anal. Calc. for $C_{25}H_{34}N_4O_8$: C, 57.90; H, 6.61; N, 10.80. Found: C, 57.73; H, 6.51; N, 10.86.

Part C. Methyl-3(R,S)-{5(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyllamine]-4-(methoxycarbonyl)pentanoate • trifluoroacetic acid salt

This product was prepared as in Example 362, Part E, using the product from Part C above (1.00 g, 1.9 mmol) to yield 0.9 g white solid; HRMS, e/z Calc. for 30 $(M+H)^+$: 419.1930. Found: 419.1921; mp = 214-215 °C (decomposes).

Example 375

-173-

Preparation of 2-(R,S)-2-Carboxymethyl-1-{5-(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-yl acetyl]piperidine

Part A. Preparation of 2-(Methoxy-2-oxoethyl)piperidine

5

Pyridylacetic acid hydrochloride (10.00 g, 57.6 mmol) and platinum(IV) oxide (1.00 g, 4.4 mmol) were shaken in a mixture of 75 ml acetic acid, 75 ml methanol, and 10 ml conc. HCl on Parr under 60 psi 10 hydrogen at room temperature overnight. The mixture was then filtered through Celite, and the filtrate evaporated under reduced pressure to yield 8.42 g (75.9%) of the title compound as an off-white solid. MS (NH₃-CI/DDIP): m/e 158 (M+H)⁺. ¹H NMR (300 MHz, CDCl₃): δ 1.50-1.96 (m, 6H); 2.80 (m, 2H); 3.20-3.60 (m, 3H); 3.76 (s, 3H). ¹³C NMR (60 MHz, d₆-DMSO): δ 21.94; 28.05; 37.46; 40.49; 44.12; 57.33; 52.74; 170.39.

Part B. Preparation of 2-(R,S)-2-(Methoxy-2-oxoethyl)-20 1-{5-(R,S)-N-[3-(4-cyanophenyl)isoxazolin-5-yl acetyl]piperidine

To 2.00 g (8.69 mmol) of 3-(4-cyanophenyl)-isoxazolin-5-yl acetic acid in 100 ml anhydrous DMF was 25 added 1.36 g (8.69 mmol) of 2-(methoxy-2-oxoethyl)piperidine, 2.80 g (8.69 mmol) of TBTU, and 6.05 ml (34.7 mmol) of diisopropylethylamine. After stirring for 6 hrs, the reaction mixture was diluted with ethyl acetate and washed with 5% aqueous citric acid solution, water, 5% aqueous NaHCO₃ solution, and saturated NaCl solution. The organic layer was dried over Na₂SO₄ and filtered. The filtrate was evaporated under reduced pressure to give the crude product as a yellow foam. Purification by flash column chromatography 30 on silica gel using 25-75% ethyl acetate in hexane 35

-174-

yielded 1.54 g (48%) of the title compound as a yellow foam. One diastereomer (racemic) was isolated from the mixture. MS (NH₃-CI/DDIP): *m/e* 370 (M+H)⁺. ¹H NMR (300 MHz, CDCl₃): δ 1.42-1.76 (m, 6H); 2.60 (m, 2H); 2.77-5 3.01 (m, 3H); 3.05-3.26 (m, 2H); 3.56-3.70 (m, 4H); 4.50 (m, 1H); 5.20 (m, 1H); 7.69 (d, *J* = 8.4 Hz, 2H); 7.77 (d, *J* = 8.4 Hz, 2H).

Part C. Preparation of 2-(Methoxy-2-oxoethyl)-1-{N-[3-(4-amidinophenyl)isoxazolin-5-yl acetyl]}piperidine,
10 (racemic diastereomer A)

HCl gas was bubbled for 2 hrs through a solution of 1.02 g (2.80 mmol) of the product of part B above in 30 15 ml of anhydrous MeOH cooled in an ice bath. The reaction flask was then sealed with Teflon tape and warmed to room temperature while stirring overnight. MeOH was evaporated under reduced pressure and then under vacuum to give the intermediate imidate as a 20 yellow foam. MS (ESI): *m/e* 402 (M+H)⁺. It was then stirred with 8.07 g (84.0 mmol) of (NH₄)₂CO₃ in 30 ml anhydrous EtOH overnight in a sealed reaction flask. After filtering, the filtrate was evaporated under reduced pressure to give the crude product as a yellow 25 foam, which was then purified by flash column chromatography using 5-17% MeOH in CH₂Cl₂ to give 0.29 g (26.8%) of the title compound as a yellow solid. MS (ESI): *m/e* 387 (M+H)⁺. ¹H NMR (300 MHz, *d*₆-DMSO): δ 1.57-1.67 (br., 6H); 2.46-2.90 (m, 5H); 3.16 (m, 2H); 30 3.53-3.64 (m, 4H); 4.36 (br. m, 1H); 5.07 (br. m, 1H); 7.89 (m, 4H); 9.38 (br. s, 3H).

Part D. Preparation of 2-Carboxymethyl-1-{N-[3-(4-amidinophenyl)isoxazolin-5-yl acetyl]}piperidine,
35 (Racemic Isomer A)

-175-

To a solution of 0.08 g (0.2 mmol) of the product isolated in Part C above in 5 ml anhydrous THF at ambient temperature was added 0.5 ml (0.5 mmol) of 1.0 M solution of NaOTMS in THF. After stirring overnight, solvent was evaporated under reduced pressure to give a yellow solid, which was recrystallized from MeOH and Et₂O to give 0.05 g (64.9%) of the title compound as a yellow powder. MS (ESI): *m/e* 373 (M+H)⁺. ¹H NMR (300 MHz, CD₃OD): δ 1.68 (br., 6H); 2.56 (m, 2H); 2.72 (m, 10 3H); 2.94 (m, 2H); 3.57 (m, 4H); 4.46 (br., 1H); 5.18 (br., 1H); 7.84 (m, 4H).

Example 377

Preparation of 2-(R,S)-2-Carboxymethyl-1-{5-(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-yl acetyl]azepine}

Part A. Preparation of 2-(R,S)-2-(Ethoxy-2-oxoethyl)-1-{5-(R,S)-N-[3-(4-cyanophenyl)isoxazolin-5-yl acetyl]}azepine

From 0.50 g (2.17 mmol) of 3-(4-cyanophenyl)isoxazolin-5-yl acetic acid, using 0.40 g (2.17 mmol) of 2-(ethoxy-2-oxoethyl)azepine, 0.70 g (2.17 mmol) TBTU, and 1.51 ml (8.70 mmol) diisopropylethylamine, 0.73 g (84.6 %) of the title compound was obtained following the procedure of Example 375, Part B. MS (NH₃-CI/DDIP): *m/e* 398 (M+H)⁺. ¹H NMR (300 MHz, CDCl₃): δ 1.26 (m, 11H); 1.83 (br., 2H); 2.05 (m, 1H); 2.18-2.65 (m, 2H); 2.76-2.85 (m, 1H); 3.04 (m, 2H); 3.62 (s, 1H); 4.08 (m, 2H); 5.22 (m, 1H); 7.68 (d, J = 8.4 Hz, 2H); 7.78 (d, J = 8.4 Hz, 2H).

Part B. Preparation of 2-(R,S)-2-(Ethoxy-2-oxoethyl)-1-{5-(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-yl acetyl]}azepine

-176-

From 0.73 g (1.84 mmol) of 2-(R,S)-2-(ethoxy-2-oxoethyl)-1-{5-(R,S)-N-[3-(4-cyanophenyl)isoxazolin-5-yl acetyl]}azepine, using EtOH as the solvent, 0.42 g (61.6%) of the title compound was obtained following the procedure of Example 375, Part C. MS (NH₃-CI/DDIP): *m/e* 415 (M+H)⁺. ¹H NMR (300 MHz, d₆-DMSO): δ 1.18 (m, 3H); 1.38 (m, 2H); 1.70 (m, 4H); 2.08 (br., 2H); 2.66 (m, 2H); 3.02-3.26 (m, 2H); 3.60 (br. m, 2H); 4.05 (m, 2H); 4.58 (m, 1H); 5.10 (m, 1H); 7.90 (m, 4H); 9.38 (br. s, 10 3H).

Part C. Preparation of 2-(R,S)-2-Carboxymethyl-1-{5-(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-yl acetyl]}azepine

From 0.16 g (0.35 mmol) of 2-(R,S)-2-(ethoxy-2-oxoethyl)-1-{5-(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-yl acetyl]}azepine and using 0.89 ml (0.89 mmol) of 1.0 M solution of NaOTMS in THF, 0.12 g (82.9%) of the title compound was obtained following the procedure of Example 375, Part D. MS (NH₃-DCI): *m/e* 387 (M+H)⁺.

Example 400

Preparation of 3-(R,S)-(Methoxy-2-oxoethyl)-4-{5-(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-yl acetyl]}piperazin-2-one

Part A. Preparation of 3-(R,S)-(Ethoxy-2-oxoethyl)-4-{5-(R,S)-N-[3-(4-cyanophenyl)isoxazolin-5-yl acetyl]}piperazin-2-one

From 1.00 g (4.34 mmol) of 3-(4-cyanophenyl)isoxazolin-5-yl acetic acid, using 0.81 g (4.34 mmol) of ethyl 2-piperazin-3-one acetate, 1.39 g (4.34 mmol) TBTU, and 3.02 ml (17.40 mmol)

-177-

diisopropylethylamine, 1.08 g (62.4 %) of the title compound was obtained following the procedure of Example 375, Part B. MS (NH₃-CI/DDIP): m/e 399 (M+H)⁺. ¹H NMR (300 MHz, CDCl₃): δ 1.26 (m, 3H); 2.71-3.65 (br., 9H); 5.87 (br. m, 1H); 4.16 (m, 2H); 5.01 & 5.09 (two t, J = 5.0, 5.1 Hz, 1H); 5.20 (m, 1H); 7.00 & 7.12 (two br., 1H); 7.77 (m, 4H).

Part B. Preparation of 3-(R,S)-(Methoxy-2-oxoethyl)-4-(5-(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-yl acetyl]piperazin-2-one

From 1.08 g (2.71 mmol) of 3-(R,S)-(ethoxy-2-oxoethyl)-4-(5-(R,S)-N-[3-(4-cyanophenyl)isoxazolin-5-yl acetyl]piperazin-2-one, 0.30 g (27.6%) of the title compound was obtained, following the procedure of Example 375, Part C. MS (ESI): m/e 402 (M+H)⁺. ¹H NMR (300 MHz, d₆-DMSO): δ 2.70-3.67 (m, 12H); 3.91 (br., 1H); 4.87 & 4.64 (two m, 1H); 5.06 (m., 1H); 7.88 (m, 4H); 8.16 (br., 1H); 9.40 (br. s, 3H).

Example 434

Preparation of (S)-N^a-[3-(4-Amidinophenyl)-isoxazolin-5-(R,S)-ylacetyl]- α -aspart-N-(2-phenylethyl)amide,

25 trifluoroacetic acid salt

Part A. Preparation of (S)-N^a-(Benzylloxycarbonyl)- β -(O-t-butyl)- α -aspart-N-(2-phenylethyl)amide

30 To a solution of (S)-N-(Benzylloxycarbonyl)- β -(O-t-butyl)-aspartic acid (BACHEM-Bioscience Inc) (3.20 g, 9.9 mmol) in DCM (25 mL), was added phenethylamine (1.34 g, 11.1 mmol); followed by DEC (2.10 g, 10.9 mmol). The reaction mixture was stirred overnight at room temperature, affording a pale yellow solution. This solution was washed with water, 1M HCl, 5% NaHCO₃ and

-178-

sat. NaCl, dried over anhydrous MgSO₄, filtered, and concentrated in vacuo to give 4.28 g (100%) of amide, which was of sufficient purity to be carried on to the next step; ¹H NMR (300 MHz, CDCl₃) δ 7.35 (s, 5H), 5 7.17-7.35 (bm, 5H), 6.52 (bs, 1H), 5.93 (bd, J = 8.1 Hz, 1H), 5.10 (s, 2H), 4.46 (bm, 1H), 3.50 (dd, J = 13.9, 6.2 Hz, 2H), 2.92 (dd, J = 17.0, 4.2 Hz, 1H), 2.78 (t, J = 7.1 Hz, 2H), 2.57 (dd, J = 17.0, 6.4 Hz, 1H), 1.42 (s, 9H); Mass Spectrum (NH₃-DCI, e/z, relative abundance) 10 444, (M+NH₄)⁺, 100%; 427, (M+H)⁺, 4%.

Part B. Preparation of (S)- β -(O-t-butyl)- α -aspart-N-(2-phenylethyl)amide

15 A solution of (S)-N-(benzyloxycarbonyl)- β -(O-t-butyl)- α -aspart-N-(2-phenylethyl)amide (4.09 g, 9.58 mmol) in ethyl alcohol (30 mL) was hydrogenated under atmospheric pressure using 10% palladium on carbon catalyst (1.0 g) for 90 minutes. The catalyst was 20 filtered and the filtrate concentrated in vacuo to give 2.80 g of an amber oil, which was purified by flash chromatography (5% MeOH/DCM), affording 2.13 g (76%) of the free amine as a solid product; ¹H NMR (300 MHz, CDCl₃) δ 7.44 (bs, 1H), 7.20-7.35 (m, 5H), 3.61 (dd, J = 25 8.4, 3.7 Hz, 1H), 3.52 (dd, J = 13.2, 7.0 Hz, 1H), 2.80-2.90 (m, 3H), 2.46 (dd, J = 16.7, 8.4 Hz, 1H), 1.58 (bs, 2H), 1.45 (s, 9H); Mass Spectrum (ESI, e/z, relative abundance) 293, (M+H)⁺, 37%; 237, (M+H-C₄H₈)⁺, 100%.

30 **Part C. Preparation of Methyl 3-(4-methoxyiminophenyl)-(5R,S)-isoxazolin-5-ylacetate. Hydrochloride Salt**

35 A suspension of 3-(4-cyanophenyl)-(5R,S)-isoxazolin-5-ylacetic acid (23.1 g, 100 mmol) in 200 mL of anhydrous methanol was chilled in an ice bath and dry

-179-

HCl gas was bubbled through the reaction mixture until a clear solution was obtained. The total addition time was about three hours. The reaction flask was sealed and the reaction mixture was allowed to warm to room temperature, with stirring, over a period of about 24 hrs. At this point, the methanolic solution was poured into 600 mL of anhydrous ether, precipitating the product, and the resulting slurry was chilled to -25°C for 2 1/2 hours. The slurry was then diluted with an additional 100 mL of chilled anhydrous ether. The precipitate was filtered, washed with two 100 mL portions of chilled anhydrous ether, and suction dried under nitrogen to afford 23.3 g (73%) of the hydrochloride salt; ¹H NMR (300 MHz, CDCl₃) δ 12.9 (bs, 1H) 12.2 (bs, 1H), 8.46 (d, J = 8.8 Hz, 2H), 7.86 (d, J = 8.8 Hz, 2H), 5.20 (bm, 1H), 4.59 (s, 3H); 3.74 (s, 3H), 3.53 (dd, J = 16.8, 10.6 Hz, 1H), 3.15 (dd, J = 16.8, 7.7 Hz, 1H), 2.90 (dd, J = 16.1, 6.2 Hz, 1H), 2.70 (dd, J = 16.1, 7.3 Hz, 1H), 1.77 (bs, 1H); Mass Spectrum (NH₃-CI/DDIP, e/z, relative abundance) 277, (M+H)⁺, 100%.

Part D. Preparation of methyl 3-(4-amidinophenyl)-(5R,S)-isoxazolin-5-ylacetate. Hydrochloride Salt

A suspension of methyl 3-(4-methoxyiminophenyl)-(5R,S)-isoxazolin-5-ylacetate hydrochloride (22.9 g, 73.0 mmol) in 500 mL of 1M ammonia in anhydrous methanol was stirred at room temperature for 14 hours during which time all solids dissolved. The solution was concentrated in vacuo to give 22.1 g (100%) of crude hydrochloride salt as a tan solid; ¹H NMR (300 MHz, CDCl₃) δ 9.6-9.2 (b), 7.91 (d, J = 8.8, 2H), 7.87 (d, J = 8.8, 2H), 5.08 (bm, 1H), 3.64 (s, 3H), 3.3-3.1 (m, 2H), 2.8 (m, 2H); Mass Spectrum (ESI, e/z, relative abundance) 264, (M+H)⁺, 100%.

-180-

Part E. Preparation of Methyl 3-(4-N-Boc-amidinophenyl)isoxazolin-5-ylacetate

5 To a solution of 21.6 g (72.5 mmol) of methyl 3-(4-amidinophenyl)isoxazolin-5-ylacetate (prepared using the procedure of Example 434, Part D) in 350 ml DMF cooled with an ice bath was added 20.2 ml (145 mmol) of triethylamine and 17.4 g (79.8 mmol) of di-tert-butyl 10 dicarbonate. The mixture was warmed to room temperature and stirred for 16 hours. The reaction mixture was poured into 1500 ml water while stirring. A white precipitate formed and was then filtered and dried on the filter under nitrogen to give 19.6 g (74.8%) of the 15 title compound as a white solid. MS (ESI): m/e 362 ($M+H$)⁺; 306 ($M+H-tBu$)⁺. ¹H NMR (300 MHz, d_6 -DMSO): δ 1.56 (s, 9H); 2.68 (dd, J = 6.1, 6.1 Hz, 1H); 2.90 (dd, J = 6.1, 6.1 Hz, 1H); 3.14 (dd, J = 6.8, 6.8 Hz, 1H); 3.56 (dd, J = 6.8, 6.8 Hz, 1H); 3.74 (s, 3H); 5.14 (m, 20 1H); 7.70 (d, J = 8.4 Hz, 2H); 7.90 (d, J = 8.4 Hz, 2H). ¹³C NMR (60 MHz, d_6 -DMSO): δ 28.46; 39.31; 39.58; 51.98; 77.89; 78.35; 126.91; 128.51; 132.79; 136.24; 156.86; 164.04; 165.76; 170.93.

25 Part F. Preparation of 3-(4-N-Boc-amidinophenyl)isoxazolin-5-ylacetic Acid

To a solution of 18.95 g (52.4 mmol) of methyl 3-(4-N-Boc-amidinophenyl)isoxazolin-5-ylacetate (prepared 30 using the procedure of Example 434, Part E) in 500 ml methanol was added 2.42 g (57.7 mmol) of lithium hydroxide monohydrate in 75 ml water at 22°C. The mixture was stirred at 22°C for 16 hours and then filtered; the filtrate was then evaporated under reduced 35 pressure to remove methanol. The residual aqueous phase was cooled with an ice bath and acidified with 6 N and 1

-181-

N HCl to pH = 4. A white solid precipitated and it was left at -4°C overnight. The solid was filtered and dried on the filter under nitrogen to give 17.74 g (97.4%) of the title compound as an off-white powder.

5 MS (ESI): m/e 348 ($M+H$)⁺; 292 ($M+H-tBu$)⁺. 1H NMR (300 MHz, d_6 -DMSO): δ 1.50 (s, 9H); 2.68 (d, J = 7.0 Hz, 2H); 3.22 (dd, J = 7.2, 7.2 Hz, 1H); 3.62 (dd, J = 6.8, 7.2 Hz, 1H); 5.04 (m, 1H); 7.78 (d, J = 8.4 Hz, 2H); 7.94 (d, J = 8.4 Hz, 2H); ^{13}C NMR (60 MHz, d_6 -DMSO): δ 28.27; 10 39.30; 40.44; 78.39; 81.55; 126.87; 129.43; 132.78; 133.87; 156.76; 158.61; 165.58; 171.91.

Part G. Preparation of (S)- Na^+ -[3-(4-N-Boc-
15 Amidinophenyl)-isoxazolin-5-(R,S)-ylacetyl]- β -(O-t-
butyl)- α -aspart-N-(2-phenylethyl)amide

To a suspension of (S)- β -(O-t-butyl)- α -aspart-N-(2-phenylethyl)amide (0.30 g, 1.0 mmol), 3-(4-N-Boc-amidinophenyl)-isoxazolin-5-ylacetic acid (0.35 g, 1.0 mmol), and TBTU (0.32 g, 1.0 mmol) in EtOAc (20 mL), was added triethylamine (460 μ L, 0.33 g, 1.0 mmol). The reaction mixture was stirred at room temperature for 4.5 hr. It was diluted with EtOAc (20 mL), washed with pH 4 buffer, water, 5% NaHCO₃ and sat. NaCl, dried over anhydrous MgSO₄, filtered, and concentrated in vacuo to give 0.58 g of solid. The crude product was purified by flash chromatography (100% EtOAc), affording 0.51 g (81%); 1H NMR (300 MHz, CDCl₃) δ 7.89 (t, J = 8.1 Hz, 2H), 7.69 (m, 2H), 7.25-7.3 (m, 3H), 7.15-7.25 (m, 4H), 7.04 (d, J = 8.4 Hz, 1H), 6.65-6.80 (dt, 1H), 5.10 (bm, 1H), 4.71 (bm, 1H), 3.4-3.7 (bm, 3H), 3.1-3.3 (octet, 1H), 2.75-2.95 (m, 3H), 2.5-2.65 (m, 3H), 1.56 (s, 9H), 1.44 (d, 9H); Mass Spectrum (ESI, e/z, relative abundance) 622, ($M+H$)⁺, 100 %.

-182-

Example 435

Preparation of (S)-N²-[3-(4-Amidinophenyl)-isoxazolin-5-ylacetyl]- α -aspart-N-(2-phenylethyl)amide, trifluoroacetic acid salt

5

A solution of (S)-N-[3-(4-N²-Boc-amidinophenyl)-isoxazolin-5-ylacetyl]- β -(O-t-butyl)- α -aspart-N-(2-phenylethyl)amide (160 mg, 0.26 mmol) in trifluoroacetic acid (10 mL) and DCM (10 mL) was stirred at room temperature for three days. The solution was concentrated in vacuo to give 150 mg of product; ¹H NMR (300 MHz, CDCl₃) δ 9.40 (bs, 2H), 9.26 (bs, 2H), 8.33 (t, J = 8.6, 1H), 7.85-8.0 (m, 1H), 7.88 (s, 4H), 7.3 (m, 1H), 7.28 (d, J = 7.1, 2H), 7.20 (d, J = 7.1, 2H), 5.07 (bm, 1H), 4.56 (bm, 1H), 3.5-3.6 (octet, 1H), 3.26 (bt, J = 7.0, 2H), 3.2 (m, 1H), 2.70 (bt, J = 7.0, 2H), 2.6-2.65 (bm, 2H), 2.4-2.5 (m, 2H); Mass Spectrum (ESI, e/z, relative abundance) 466, (M+H)⁺, 100%.

20

Examples 473A and 473B

Resolution of Methyl N²-3-methylphenylsulfonyl-N³-[3-(4-amidinophenyl)-5S-ylacetyl]-S-2,3-diaminopropionate trifluoroacetic and Methyl N²-3-methylphenylsulfonyl-N³-[3-(4-amidinophenyl)-5R-ylacetyl]-S-2,3-diaminopropionate hydrochloride

The mixture was initially purified on a Pirkle DNBPG column using 10%HOAc/20%EtOH/70% hexane as the eluting solvent. The column temperature was maintained at 45°C, the flow rate at 1.5ml/min, and the detector set at 280nm. The diastereomers were then separated on a chiralcel OD-25 X 2cm column using an eluting solvent of 0.1%TFA/20%MeOH/80%CO₂. The column temperature was maintained at 30°C, the flow rate at 13ml/min, the

-183-

pressure at 175 atm, and the detector was set at 280nm. Injections were made on 23mg of sample. Over the two columns a total of 300mg was injected giving 59mg of the R isomer, Ex. 473A (HRMS calc'd for C₂₃H₂₇N₅O₆S 5 502.176031 Found: 502.175508) and 85mg of the S isomer, Ex. 473B (HRMS calc'd for C₂₃H₂₇N₅O₆S. 502.176031 Found: 502.176358).

Example 473C

10 N²-3-methylphenylsulfonyl-N³-[3-(4-amidinophenyl)-5S-ylacetyl]-S-2,3-diaminopropionic acid

Part A: Methyl-N²-3-methylphenylsulfonyl-N³-[3-(4-cyanophenyl)-5S-ylacetyl]-S-2,3-diaminopropionate

15 Into a solution of 3-(4-cyanophenyl)isoxazolin-5-S-ylacetic acid (1.82g, 7.90mmol, obtained as described in Es. 314A, part F) in DMF (50ml) was added methyl-N²-3-methylphenylsulfonyl-L-2,3-diaminopropionate HCl salt (2.77g, 7.90mmol), TBTU (2.53g, 7.90mmol), and Hünigs 20 base (2.75ml, 15.8mmol). After stirring at room temperature for 16 hours, the reaction mixture was diluted with EtOAc (500ml) and washed one time with water (200ml), one time with sat'd NaHCO₃ (200ml), one time with 0.1N HCl (200ml), dried (MgSO₄), filtered, and 25 concentrated. Column chromatography on silica gel using 10% EtOAc/hexane as the eluting solvent gave 1.99g (52%) of the desired material as an off-white foam. ¹H NMR: (CDCl₃): δ 7.81-7.78 (d, 2H, J=8.4Hz); 7.16-7.67 (d, 2H, J=8.8Hz); 7.61-7.58 (m, 2H); 7.39-7.37 (d, 2H, J=5.1Hz); 6.35-6.30 (m, 1H); 5.54-5.52 (d, 1H, J=7.7Hz); 5.18-5.17 (m, 1H); 4.00-3.96 (m, 1H); 3.62-3.50 (m, 3H); 3.57 (s, 3H); 3.27-3.19 (dd, 1H, J=7.7, 17.0Hz); 2.78-3.70 (dd, 1H, J=5.9, 14.8Hz); 2.64-2.57 (dd, 1H, J=6.6, 14.6Hz); 2.42 (s, 3H).

-184-

Part B: Methyl-N²-3-methylphenylsulfonyl-N³-[3-(4-amidinophenyl)-5S-ylacetyl]-S-2,3-diaminopropionate hydrochloride

5 Methyl-N²-3-methylphenylsulfonyl-N³-[3-(4-cyanophenyl)-5S-ylacetyl]-S-2,3-diaminopropionate was dissolved in 100ml absolute ethanol at 0°C and a stream of HCl gas was bubbled through the solution for two hours. The reaction vessel was sealed and after sitting at room temperature for 16 hours the volatiles were 10 removed *in vacuo*. The residue was then diluted with 100ml of absolute ethanol, ammonium carbonate (9.6g, 0.123mol) was added and after stirring for 16 hours the reaction mixture was filtered and concentrated *in vacuo*.

Column chromatography on silica using a gradient elution 15 from 5%MeOH/CH₂Cl₂ to 20%MeOH/CH₂Cl₂ gave 0.762g (37%) of the desired amidine as a white solid. ¹H NMR (CDCl₃): δ 8.23-8.20 (m, 1H); 7.91-7.85 (m, 4H); 7.57-7.54 (m, 2H); 7.49-7.46 (m, 2H); 5.00-4.94 (m, 1H); 4.08-3.86 (m, 1H); 3.59-3.49 (m, 1H); 3.39 (s, 3H); 3.38-3.29 (m, 3H); 2.49 20 (s, 3H); 2.50-2.45 (m, 2H). HRMS: calc'd for C₂₃H₂₇N₅O₆S: 502.176031 found 502.175992. [α]_D = +48.88° (c=0.180, MeOH).

Part C: N²-3-methylphenylsulfonyl-N³-[3-(4-amidinophenyl)-5(S)-yl]acetyl-S-2,3-diaminopropionic acid

25 The compound of Ex 473C, part B (0.077 g., 0.14 mmol) was dissolved in MeOH (4ml). To the resulting solution was added a solution of lithium hydroxide (0.0066 g., 0.158 mmol) in water (4 ml) and the mixture was stirred overnight at room temperature. The methanol 30 was removed by evaporation *in vacuo*, and the product precipitated from the aqueous as a white solid (0.026 g., 35%). HRMS calcd for C₂₂H₂₅N₅O₆S: 488.160381; found: 488.160827.

Example 473D

-185-

Methyl-N²-3-methylphenylsulfonyl-N³-[3-(4-
amidinophenyl)-5R-ylacetyl]-S-2,3-diaminopropionate
hydrochloride

5 Part A: Methyl-N²-3-methylphenylsulfonyl-N³-[3-(4-
cyanophenyl)-5R-ylacetyl]-S-2,3-diaminopropionate

This compound was synthesized from 3-(4-cyanophenyl)isoxazolin-5-(R)-ylacetic acid (3.07g, 0.011mol, obtained as described in Ex. 314B, part B) 10 using the same procedure as for example 473C, part A. Yield 41%. Theory: C 57.02, H 4.99, N 11.56. Found: C 56.83, H 4.87, N 11.45.

15 Part B: Methyl-N²-3-methylphenylsulfonyl-N³-[3-(4-
amidinophenyl)-5R-ylacetyl]-S-2,3-diaminopropionate
hydrochloride

This compound was synthesized from Methyl-N²-3-methylphenylsulfonyl-N³-[3-(4-cyanophenyl)-5R-ylacetyl]-S-2,3-diaminopropionate using the same procedure as for 20 example 473C, part B. Yield 49%. HRMS Calc'd for C₂₃H₂₇N₅O₆S 502.176031 Found: 502.174103.

Example 496

25 Methyl N²-(2,2-diphenyl-1-ethenesulfonyl)-N³-[3-(4-
amidinophenyl)isoxazolin-5-(R,S)-ylacetyl]-S-2,3-
diaminopropionate, trifluoroacetic acid salt

Part A: Methyl N²-(2,2-diphenyl-1-ethenesulfonyl)-N³-
Boc-(S)-2,3-diaminopropionate.

30 To a mixture of methyl N³-Boc-(S)-2,3-diaminopropionate (255 mg, 1.17 mmol) and 2,2-diphenylethylenesulfonyl chloride (Hasegawa and Hirooka, J. Chem. Soc: Japan 48, 1513-1518 (1975); 391 mg, 1.40 mmol) in methylene chloride (10 mL) cooled in an ice bath was added triethylamine (0.25 mL, 1.76 mmol).

-186-

After 22 h, the mixture was concentrated and flash chromatographed (6:4 toluene/ethyl acetate) to provide 240 mg (46%) of product. NMR (CDCl₃) δ 7.42-7.20 (10H), 6.81 (s, 1H), 5.24 (bd, 1H), 4.87 (bs, 1H), 3.95 (q, 1H), 5 3.72 (s, 3H), 3.50-3.42 (2H), 1.44 (s, 9H); mass spec (NH₃-CI) m/z 466.54 (M+NH₄⁺, 100%).

Part B: Methyl N²-(2,2-diphenyl-1-ethenesulfonyl)-(S)-2,3-diaminopropionate TFA salt.

10 The product of Part A (210 mg, 0.468 mmol) was dissolved in 5 mL of methylene chloride and 3 mL TFA. After 1 hour, the solution was concentrated to give an oily product. (222 mg, 100%). NMR (DMSO-d₆) δ 8.02 (bs, 3H), 7.40 (m, 5H), 7.23 (m, 4H), 7.00 (s, 1H), 4.26 (m, 1H), 3.71 (s, 3H), 3.20 (m, 1H), 2.98 (m, 1H).

Part C: Methyl N²-(2,2-diphenyl-1-ethenesulfonyl)-N³-(4-N-Boc-amidinophenyl)isoxazolin-5-(R,S)-ylacetyl-(S)-2,3-diaminopropionate.

20 The product of part B (220 mg, 0.46 mmol) was reacted with 3-(4-N-Boc-amidinophenyl)-isoxazolin-5-ylacetic acid (from Example 434, part F; 160 mg, 0.46 mmol), according to the procedure of example DGB-1, Part A, to provide the title product (215 mg, 68%). NMR (CDCl₃) δ 7.84 (m, 2H), 7.64 (m, 2H), 7.40-7.18 (10H), 6.75 (s, 1H), 6.30 (m, 1H), 5.30 (m, 1H), 5.04 (m, 1H), 4.00 (1H), 3.78 (s, 3H), 3.62-3.40 (4H), 3.10 (m, 1H), 2.70-2.50 (2H), 2.04 (s, 1H), 1.58 (s, 9H); mass spec (ESI) m/z 690.2 (M+H⁺, 100%).

30 Part D: Methyl N²-(2,2-diphenyl-1-ethenesulfonyl)-N³-(4-amidinophenyl)isoxazolin-5-(R,S)-ylacetyl-(S)-2,3-diaminopropionate, trifluoroacetic acid salt

The product of part C (210 mg, 0.30 mmol) was dissolved in methylene chloride (3 mL) and treated with

-187-

trifluoroacetic acid (1 mL) according to the procedure of example DGB-1, Part B, to provide the title product (150 mg, 80%). NMR (DMSO-d₆) δ 9.39 (bs, 2H), 9.05 (bs, 2H), 8.22 (m, 1H), 8.00 (m, 1H), 7.85 (s, 4H), 7.40 (m, 6H), 7.20 (m, 4H), 6.89 (s, 1H), 5.00 (m, 1H), 4.00 (m, 1H), 3.70-3.18 (5H), 3.62 (2s, 3H); mass spec (ESI) m/z 590.2 (M+H⁺, 100%)

Example 511.

10 Methyl N²-(N,N-dimethylsulfamoyl)-N³-(3-(4-aminophenyl) isoxazolin-5-(R,S)-ylacetyl)-S-(S)-2,3-diaminopropionate, trifluoroacetic acid salt

15 Part A: Methyl N²-(N,N-dimethyl sulfamoyl)-N³-Boc-(S)-2,3-diaminopropionate.

To a mixture of methyl N³-Boc-(S)-2,3-diaminopropionate (400 mg, 1.80 mmol) and Dimethylsulfamoyl chloride (0.24 mL, 2.20 mmol) in methylene chloride (10 mL) cooled in an ice bath was 20 added triethylamine (0.38 mL, 2.20 mmol). After 18 h, the mixture was concentrated and flash chromatographed (6:4 toluene/ethyl acetate) to provide 283 mg (49%) of product. NMR (CDCl₃) δ 5.23 (bd, 1H), 4.90 (m, 1H), 4.06 (m, 1H), 3.80 (s, 3H), 3.52 (bt, 2H), 2.80 (s, 6H), 1.42 (s, 9H); mass spec (NH₃-CI) m/z 343.0 (M+NH₄⁺, 100%).

Part B: Methyl N²-(N,N-dimethyl sulfamoyl)-(S)-2,3-diaminopropionate TFA salt.

The Product of Part A was dissolved in 5 mL of 30 methylene chloride and 3 mL TFA. After 1 hour, the solution was concentrated to give an oily product (294 mg, 100%). NMR (DMSO-d₆) δ 6.52 (bs, 2H), 4.4-3.9 (2H), 3.8 (bs, 3H), 2.93 (bs, 6H).

-188-

Part C: Methyl N²-(N,N-dimethyl sulfamoyl)-N³-[3-(4-N-Boc-amidinophenyl)isoxazolin-5-(R,S)-ylacetyl]-L-2,3-diaminopropionate.

The product of part B (200 mg, 0.61 mmol) was 5 reacted with 3-(4-N-Boc-amidinophenyl)isoxazolin-5-ylacetic acid (from Example 434, part F; 212 mg, 0.61 mmol), according to the procedure of DGB-1, Part A, to provide the title product (203 mg, 61%). NMR (CDCl₃) δ 7.78 (m, 2H), 7.42 (bt, 2H), 7.00 (m, 1H), 5.92 (m, 1H), 10 5.04 (m, 1H), 3.80 (2s, 3H), 3.64 (m, 2H), 3.40 (m, 1H), 3.05 (m, 1H), 2.80 (2s, 6H), 2.74 (m, 1H), 2.60 (m, 1H), 2.02 (s, 3H), 1.60 (s, 9H); mass spec (ESI) m/z 555.1 (M+H⁺, 100%).

15 Part D: Methyl N²-(N,N-dimethyl sulfamoyl)-N³-[3-(4-amidinophenyl)isoxazolin-5-(R,S)-ylacetyl]-L-2,3-diaminopropionate, trifluoroacetic acid salt

The product of part C (183 mg, 0.329 mmol) was dissolved in methylene chloride (3 mL) and treated with 20 trifluoroacetic acid (1 mL), according to the procedure of example DGB-1, Part B, to provide the title product (159 mg, 85%). NMR (DMSO-d₆) δ 9.40 (bs, 2H), 9.00 (bs, 2H), 8.22 (m, 1H), 7.82 (s, 4H), 5.00 (m, 1H), 3.95 (m, 1H), 3.68 (2s, 3H), 3.60 (m, 2H), 3.20 (m, 4H), 2.80 (s, 6H); mass spec (ESI) m/z 455.1 (M+H⁺, 100%).

Example 512

Methyl N²-(m-toluenesulfonyl)-N³-[3-(4-amidino-2-fluorophenyl)isoxazolin-5-ylacetyl]-S-2,3-diaminopropionate hydrochloric acid salt

Part A: 3-Fluoro-4-methylbenzamide

3-Fluoro-4-methylbenzoic acid (10 g, 65 mmol) was boiled in thionyl chloride (100 mL) under a drying tube 35 for 2.5 h. The excess SOCl₂ was removed by distillation. The oily acid chloride product was

-189-

diluted with CH_2Cl_2 (100 mL) and cooled in an ice bath. Conc. aq. NH_3 (20 mL) was added dropwise, and stirring continued at 0 °C for 0.5 h. The CH_2Cl_2 was removed in vacuo, then the residue was diluted with EtOAc. The mixture was extracted with sat. aq. Na_2CO_3 (2x), H_2O , and brine, dried (MgSO_4), and concentrated to yield 9.9 g of a pale yellow solid; mp 161-163 °C; IR(KBr) 3382, 1654 cm^{-1} ; Anal. Calc. for $\text{C}_8\text{H}_8\text{FNO}$: C, 62.74; H, 5.27; N, 9.15; F, 12.40. Found: C, 62.66; H, 5.17; N, 9.12; F, 12.28.

Part B: 3-Fluoro-4-methylbenzonitrile

A solution of trichloroacetyl chloride (7.3 mL, 65 mmol) in CH_2Cl_2 (20 mL) was added dropwise over 0.5 h to a solution/suspension of the Part A amide (9.0 g, 59 mmol) and Et_3N (17 mL, 120 mmol) in CH_2Cl_2 (80 mL) at 0 °C. After 40 min, the mixture was concentrated in vacuo, then diluted with Et_2O . This solution was extracted with 1 M HCl, sat. aq. NaHCO_3 , H_2O , and brine, then dried (MgSO_4), and concentrated to yield 7.8 g of a tan solid; mp 45-47 °C; IR(KBr) 2232 cm^{-1} ; HRMS, e/z Calc. for $(\text{M}+\text{H})^+$: 135.0484. Found: 135.0482.

Part C: 2-Fluoro-4-cyanobenzylbromide

N-Bromosuccinimide (9.6 g, 54 mmol) and the part B substrate (7.3 g, 54 mmol) were heated under reflux in CCl_4 (100 mL) under N_2 with irradiation with a high intensity visible lamp for 2 h. After cooling to ambient temp., the mixture was filtered through a Celite pad and concentrated in vacuo. The crude product was recrystallized from hot cyclohexane (4x) to yield 4.5 g of off-white needles; mp 75-77 °C; IR(KBr) 2236 cm^{-1} ; HRMS, e/z Calc. for $(\text{M}+\text{H})^+$: 213.9668. Found: 213.9660.

35

Part D: 2-Fluoro-4-cyanobenzaldehyde

-190-

The part C benzyl bromide (3.68 g, 17 mmol), trimethylamine N-oxide dihydrate (7.6 g, 68 mmol), CH₂Cl₂ (15 mL), and DMSO (30 mL) were stirred at 0 °C for a few h, slowly warming to ambient T overnight. The 5 mixture was diluted with water (30 mL) and brine (30 mL), and extracted with Et₂O (4x). The combined organics were washed with brine, dried (MgSO₄), and concentrated to yield 1.1 g of a yellow solid; IR(KBr) 2238, 1706 cm⁻¹; HRMS, e/z Calc. for (M+H)⁺: 10 150.0355. Found: 150.0341.

Part E: 2-Fluoro-4-cyanobenzaldoxime

The part D aldehyde (1.1 g, 7.4 mmol), hydroxylamine hydrochloride (1.0 g, 15 mmol), K₂CO₃ (1.0 15 g, 7.4 mmol), water (1 mL), and MeOH (10 mL) were heated under reflux for 2.25 h. After brief cooling, the mixture was diluted with water, and the insoluble product was collected by filtration, then rinsed with more water. Drying under high vacuum provided 0.94 g of 20 a pale yellow amorphous solid; mp 179-182 °C; IR(KBr) 3256, 2236, 1556 cm⁻¹; HRMS, e/z Calc. for (M+H)⁺: 165.0464. Found: 165.0455.

25 Part F: Methyl 3-(4-cyano-2-fluorophenyl)isoxazolin-5-ylacetate

The part E oxime was allowed to react with Clorox and methyl vinylacetate in the usual way to afford the isoxazoline as a yellow solid in 32% yield; mp 92-94 °C; IR(KBr) 2240, 1746 cm⁻¹; HRMS, e/z Calc. for 30 (M+H)⁺: 263.0832. Found: 263.0818. Anal. Calc. for C₁₃H₁₁FN₂O₃: C, 59.54; H, 4.23; N, 10.68; F, 7.24. Found: C, 59.84; H, 4.31; N, 10.53; F, 7.26.

35 Part G: Methyl N²-(*m*-toluenesulfonyl)-N³-[3-(4-amidino-2-fluorophenyl)isoxazolin-5-ylacetyl]-S-2,3-diaminopropionate hydrochloric acid salt

-191-

The part F intermediate was converted to the title compound via the usual sequence of steps: Pinner amidine synthesis, amidine BOC protection, ester saponification, condensation with the 2,3-5 diaminopropionate sulfonamide ester, and BOC deprotection to provide a yellow gum; HRMS, e/z Calc. for $(M+H)^+$: 520.1666. Found: 520.1675.

Example 513

10 Methyl N²-(n-butyloxycarbonyl)-N³-[3-(3-amidinopyrid-6-yl)isoxazolin-5-ylacetyl]-S-2,3-diaminopropionate bis hydrochloric acid salt

Prepared using methods described in Ex. 514 to
15 provide a pale yellow powder; mp 90-110 °C (dec);
HRMS, e/z Calc. for $(M+H)^+$: 449.2149. Found:
449.2140.

Example 514

20 Methyl N²-(m-toluenesulfonyl)-N³-[3-(3-amidinopyrid-6-yl)isoxazolin-5-ylacetyl]-S-2,3-diaminopropionate bis hydrochloric acid salt

Part A: 3-cyano-6-pyridaldoxime

25 5-Cyano-2-picoline (25 g, 0.21 mol) and I₂ were heated under reflux in DMSO (200 mL) for 1 h. After cooling to RT, hydroxylamine hydrochloride (16 g, 0.23 mol), K₂CO₃ (29 g, 0.21 mol), and water (21 mL) were added. The resulting mixture was heated to 80 °C for
30 2.5 h, cooled, diluted with water (100 mL) and much acetone, and absorbed onto silica gel by concentration. Chromatography on silica gel, eluting with 0% to 50% EtOAc in hexane, afforded 12.2 g of a tan solid; mp 204-207 °C (dec); HRMS, e/z Calc. for $(M+H)^+$:
35 148.0511. Found: 148.0516.

-192-

Part B: Methyl 3-(3-cyanopyrid-6-yl)isoxazolin-5-ylacetate

The oxime of Ex. 514, part A was converted to the isoxazoline as described in Ex. 516, part B in 76% yield as a yellow solid; mp 97-98 °C; HRMS, e/z Calc. for (M+H)⁺: 246.0879. Found: 246.0881. Anal. Calc. for C₁₂H₁₁N₃O₃: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.74; H, 4.51; N, 17.11.

10 Part C: Methyl 3-(3-t-butyloxycarbonylamidinopyrid-6-yl)isoxazolin-5-ylacetate

The nitrile of Ex. 514, part B was converted to the amidine as described in the method of Ex. 516, parts D & E (except that 0.6 eq. NaOMe was required), and BOC 15 protected in standard fashion to afford, after purification, a yellow solid; mp 143 °C (gas evolves); HRMS, e/z Calc. for (M+H)⁺: 363.1668. Found: 363.1675. Anal. Calc. for C₁₇H₂₂N₄O₅: C, 56.35; H, 6.12; N, 15.46. Found: C, 56.35; H, 6.10; N, 15.39.

20 Part D: Lithium 3-(3-t-butyloxycarbonylamidinopyrid-6-yl)isoxazolin-5-ylacetate

The ester of Ex. 514, part C was saponified and lyophilized as described in the method of Ex. 516, part 25 F to give a colorless amorphous solid quantitatively; mp >230 °C; HRMS, e/z Calc. for conjugate acid (M+H)⁺: 349.1512. Found: 349.1527.

30 Part E: Methyl N²-(*m*-toluenesulfonyl)-N³-(3-amidinopyrid-6-yl)isoxazolin-5-ylacetyl-L-S-2,3-diaminopropionate bis hydrochloric acid salt

The part D lithium carboxylate was converted to the title compound by treatment with HCl in MeOH to provide a yellow solid; mp 90 °C (dec); HRMS, e/z Calc. for 35 (M+H)⁺: 503.1713. Found: 507.1718.

-193-

Example 515

Methyl N²-(n-butyloxycarbonyl)-N³-[3-(2-amidinopyrid-5-yl)isoxazolin-5-yl]acetyl]-S-2,3-diaminopropionate bis hydrochloric acid salt

5

In similar fashion to the method described in Ex. 516, the compound of Ex. 514, part E was coupled with methyl N²-(n-butyloxycarbonyl)-2,3-diaminopropionate hydrochloride using conditions described above, followed by BOC deprotection with 4 M HCl/dioxane to yield a pale yellow powder; HRMS, e/z Calc. for (M+H)⁺: 449.2149. Found: 449.2154.

15

Example 516

Methyl N²-(m-toluenesulfonyl)-N³-[3-(2-amidinopyrid-5-yl)isoxazolin-5-yl]acetyl]-S-2,3-diaminopropionate bis hydrochloric acid salt

20 Part A: 2-Chloro-5-pyridaldoxime

2-Chloro-5-formylpyridine (2.1 g, 15 mmol) was condensed with hydroxylamine hydrochloride in the usual way to give the oxime, 1.5 g, as a yellow crystalline solid; mp 171-175 °C (dec); HRMS, e/z Calc. for (M+H)⁺: 157.0169. Found: 157.0175.

25

Part B: Methyl 3-(2-chloropyrid-5-yl)isoxazolin-5-ylacetate

30

Clorox (20 mL) was added dropwise over 1.75 h to a mixture of the part A oxime (1.13 g, 7.2 mmol), methyl vinylacetate (70% purity, 3.0 g, 21 mmol), CH₂Cl₂ (40 mL), and DMF (4 mL) with stirring at ambient temperature. The CH₂Cl₂ was evaporated, and the mixture was diluted with EtOAc, extracted with water (5x) and

-194-

brine, then dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica gel, eluting with 0% to 70% EtOAc in hexane, afforded 1.4 g of a solid; mp 94-96 °C; HRMS, e/z Calc. for $(M+H)^+$: 255.0536. Found: 5 255.0531.

Part C: Methyl 3-(2-cyanopyrid-5-yl)isoxazolin-5-ylacetate

The part B chloropyridine (0.51 g, 2.0 mmol), zinc 10 cyanide (0.23 g, 2.0 mmol), $Pd(PPh_3)_4$ (0.12 g, 0.10 mmol), and DMF (2 mL) were heated to 80 °C under N_2 for 3 days. After cooling and concentration, the mixture was preabsorbed onto silica gel by concentration from $CHCl_3$. Chromatography on silica gel, eluting with 0% to 15 90% EtOAc in hexane afforded 0.28 g of a pale yellow solid; mp 115-116 °C; HRMS, e/z Calc. for $(M+H)^+$: 246.0879. Found: 246.0880. Anal. Calc. for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.68; H, 4.48; N, 16.90.

20

Part D: Methyl 3-(2-amidinopyrid-5-yl)isoxazolin-5-ylacetate formic acid salt

The part C cyanopyridine (0.47 g, 1.9 mmol) and 25 sodium methoxide (prepared *in situ* from Na metal, 4 mg, 0.2 mmol) were stirred in dry MeOH (6 mL) at ambient temperature for 16 h, after which 1H NMR analysis of a reaction aliquot indicated complete formation of methyl imidate [note 9.25 (s, 1H) and 3.92 (s, 3H)]. Ammonium formate (0.60 g, 9.5 mmol) was added to the reaction 30 mixture, and stirring continued for 7 h. The mixture was absorbed onto silica gel by concentration *in vacuo*. Chromatography on silica gel, eluting with 0% to 20% MeOH in $CHCl_3$, and concentration afforded 0.61 g of the amidine as an off-white solid; mp 180-182 °C (dec); 35 HRMS, e/z Calc. for $(M+H)^+$: 263.1144. Found: 263.1148.

Part E: Methyl 3-(2-t-butyloxycarbonylamidinopyrid-5-yl)isoxazolin-5-ylacetate

The part D amidine was BOC protected in standard fashion to afford, after silica gel chromatographic purification, a 41% yield of a colorless foam; HRMS, e/z Calc. for $(M+H)^+$: 363.1668. Found: 363.1682.

Part F: Lithium 3-(2-t-butyloxycarbonylamidinopyrid-5-yl)isoxazolin-5-ylacetate

The part E methyl ester (0.37 g, 1.0 mmol) was saponified by stirring with 0.5 M LiOH in MeOH at RT. The MeOH was removed *in vacuo*, then the aqueous mixture was frozen and lyophilized to produce a pale yellow solid quantitatively; HRMS, e/z Calc. for conjugate acid $(M+H)^+$: 349.1512. Found: 349.1531.

Part G: Methyl N²-(*m*-toluenesulfonyl)-N³-[3-(2-amidinopyrid-5-yl)isoxazolin-5-ylacetyl]-S-2,3-diaminopropionate bis hydrochloric acid salt

The part F lithium carboxylate was condensed with methyl N²-(*m*-toluenesulfonyl)-2,3-diaminopropionate hydrochloride using conditions described above, followed by standard BOC deprotection with 4 M HCl/dioxane to yield a yellow amorphous solid; HRMS, e/z Calc. for $(M+H)^+$: 503.1713. Found: 503.1707.

Example 548

Preparation of 3-bromothiophene-2-sulfonyl chloride

A solution of chlorosulfonic acid (14.3 g, 0.12 mol) in 35 mL of 1,2-dichloroethane was chilled to -10°C and protected from moisture. Phosphorus pentachloride (20.8 g, 0.1 mol) was added in small portions while maintaining the temperature between -5° and -10°C. The resulting slurry was stirred at -10°C for 30 minutes. Then, 3-bromothiophene (16.3 g, 0.1 mol) was added

-196-

dropwise over a period of 45 minutes, maintaining the temperature between -5° and +5°C. During the addition of the 3-bromothiophene, hydrogen chloride gas was evolved; the reaction mixture became thick and pasty, 5 and difficult to stir. Upon complete addition of the 3-bromothiophene, the reaction temperature was held at 0°C for two hours. The reaction was then heated to 80°C and kept there for one hour; during which the solids dissolved, and hydrogen chloride gas was evolved once 10 more. The reaction mixture was chilled in an ice bath, poured over 250 g crushed ice, and stirred for one hour as the ice melted. The resulting two phase system was separated and the aqueous layer washed three times with 125 mL of chloroform. The combined organic phases were 15 dried over anhydrous MgSO₄, filtered, and concentrated in vacuo to give 24.1 g (92%) of crude product as a dark amber oil; ¹H NMR (300 MHz, CDCl₃) δ 7.22 (d, J = 5.3, 1H), 7.73 (d, J = 5.3, 1H); Mass Spectrum (CH₄-DCI / GC-MS, e/z, relative abundance) 262.8, (M+H)⁺, 100%; 226.9, 20 (M+H-HCl)⁺, 89.7%.

Example 587A

25 N²-3-methylphenylsulfonyl-N³-[3-(4-amidinophenyl)-5S-ylacetyl]-S-2,3-diaminopropionic acid

The compound of Example 473C, Part B (0.077g, 0.14mmol) was dissolved in MeOH (4ml), LiOH (0.0066g, 0.158mmol) 30 in H₂O (4ml) was added and the reaction mixture left to stir overnight. After evaporation of methanol the product precipitated from the aqueous as a white solid (0.027g, 35% yield). HRMS calc'd for C₂₂H₂₅N₅O₆S: 488.160381 found: 488.160827.

35

Example 602

-197-

Methyl N²-n-butyloxycarbonyl-N³-[3-(4-guanidinophenyl)isoxazolin-5-(R,S)-ylacetyl]- (S)-2,3-diaminopropionate, trifluoroacetic acid salt

Part A: [3-[(4-t-butyloxycarbonylamino)phenyl]-

5 isoxazolin-5-ylacetic acid: This compound was prepared in 49% yield from 4-t-butyloxycarbonylaminobenzaldoxime and t-butyl vinyl acetate using the procedure described above for Ex. 275, Part A. ¹HNMR(CDCl₃) δ 0.99 (t, 3H), 1.35 (m, 2H), 1.50 (s, 9H), 1.61 (m, 2H), 2.60 (dd, J = 7.7 and 16.5 Hz, 1H) 2.84 (dd, J = 5.9 & 16Hz, 1H), 3.06 (dd, J = 7.4 & 16.9 Hz, 1H), 3.48 (dd, J = 10.3 & 16.5Hz, 1H), 4.10 (t, 2H), 5.03 (m, 1H), 6.60 (broad s, 1H), 7.38 (d, J = 8.4 Hz, 2H), 7.58 (J = 8.3Hz, 2H); IR(KBr): 2966, 1734, 1740, 1610, 1578, 1528, 1508, 1458, 1442, 1412, 1392, 1368 1234, 1160, 1058, 916, 878, 828, 772, 612 cm⁻¹; HRMS calcd. for C₂₀H₂₈N₂O₅: 377.207647, Found 377.207278. Standard LiOH saponification conditions then afforded the corresponding carboxylic acid compound as colorless crystals in 88% yield. mp 20 178-180°C; ¹HNMR(CDCl₃) δ 1.52 (s, 9H), 2.67 (dd, J = 7.8 and 16 Hz, 1H), 2.89 (dd, J = 8.3 & 16Hz, 1H), 3.06 (dd, J = 9.5 & 16.9 Hz, 1H), 3.48 (dd, J = 10.3 & 16.5z, 1H), 5.03(m, 1H).

Part B: Methyl N²-n-butyloxycarbonyl-N³-[3-[(4-t-butyloxycarbonylamino)phenyl]isoxazolin-5-yl acetyl]- (S)-2,3-diaminopropionate: The compound of Example 602,

Part A was condensed with methyl N²-tBoc-(S)-2,3-diaminopropionate using the procedure described for Ex. 275, Part C above to provide the desired product. mp 30 80-82°C; ¹HNMR(CDCl₃) δ 1.88 (t,3H), 1.30 (m,2H), 1.47 (sm,20H), 2.50 (dd,1H), 2.61(dd, 1H), 3.07 (dd,1H), 3.40 (dd,1H), 3.63 (t,2H), 3.74 (s,3H), 4.00 (m,2H), 4.38 (m,1H), 5.00 (m,1H), 5.88 (dd,1H), 6.77 (t,1H), 7.58 (d,2H), 7.84 (d,2H), 10.4 (s,1H), 11.6 (s,1H); 35 IR(KBr):3286, 2964, 1722, 1646, 1546, 1414, 1368, 1340,

-198-

1312, 1294, 1240, 1156, 1122, 1100, 1058, 1030, 844, 776
cm⁻¹. Mass spectrum (CI/NH₄) 663(M+H,20), 563(7),
549(78), 506(81), 463(100)..

5 Part C: Methyl N²-n-butyloxycarbonyl-N³-[3-(4-
guanidinophenyl)isoxazolin-5-yl acetyl]-[S]-2,3-
diaminopropionate: The compound of Ex 602, part B was
treated with TFA in dichloromethane to afford the
corresponding aniline as its TFA salt. This
intermediate was converted to the corresponding bis-BOC
10 protected quanidino compound in 59% yield using the
method of Kim et al. (Tet. Lett. 1993, 48, 7677).
Deprotection under standard conditions (TFA/CH₂Cl₂)
provided the title compound as its TFA salt (90%).

15 ¹HNMR (DMSO-d₆) δ 1.89 (t, 3H), 1.34 (m, 2H), 1.57 (m, 2H),
3.40 (m, 2H), 3.65 (m, 1H), 3.70 (s, 3H), 4.00 (t, 2H), 4.31
(m, 1H), 5.02 (m, 1H), 6.80 (m, 1H), 7.28 (d, 2H), 7.64
(broads, 3H), 7.68 (d, 2H), 7.84 (broad, 1H); Mass
spectrum(ES) m/z 463 (M+H, 100).

20

Example 651

25 Methyl N²-benzyloxycarbonyl-N³-methyl-N³-[3-(4-
amidinophenyl)isoxazolin-5-(R,S)-yl acetyl]-[S]-2,3-
diaminopropionate, trifluoroacetic acid salt

20

Part A. Preparation of methyl N²-benzyloxycarbonyl-N³-
methyl-[3-(4-N-Boc-amidinophenyl)isoxazolin-5-(R,S)-
yl acetyl]-[S]-2,3-diaminopropionate.

30 To a mixture of 3-(4-N-Boc-amidinophenyl)-
isoxazolin-5-ylacetic acid (prepared according to the
procedure of Example 434, part F; 189 mg, 0.54 mmol),
methyl N³-methyl-N²-Cbz-L-2,3-diaminopropionate
(prepared according to Sakai and Ohfune, J. Am. Chem.
Soc. 114, 998 (1992); 145 mg, 0.54 mmol) and TBTU (175
35 mg, 0.54 mmol) in ethyl acetate (10 mL) was added

-199-

triethylamine (0.15 mL, 1.09 mmol). After stirring for 26 h, the mixture was diluted with ethyl acetate, washed with pH 4 buffer, then with saturated aqueous sodium bicarbonate, then with saturated brine. The organic phase was dried ($MgSO_4$) and concentrated. The residue was flash chromatographed (ethyl acetate) to provide the product as a colorless glass (279 mg, 86%): NMR ($CDCl_3$) δ 7.88 (m, 2H), 7.69 (m, 2H), 5.79 (bd, 1H), 5.09 (m, 3H), 4.58 (m, 1H), 3.86 (m, 1H), 3.77 (2s, 3H), 3.63 (m, 2H), 3.14 (dd, 1H), 3.01 (2s, 3H), 2.9 (m, 1H), 2.53 (m, 1H), 1.66 (b, 2H), 1.56 (s, 9H); mass spec (ESI) m/z 596.2 ($M+H^+$, 100%).

15 Part B. Preparation of Methyl N^2 -benzyloxycarbonyl- N^3 -methyl- N^3 -[3-(4-amidinophenyl)isoxazolin-5-(R,S)-ylacetyl]-S-2,3-diaminopropionate, trifluoroacetic acid salt

The product of part A (226 mg, 0.38 mmol) was dissolved in dichloromethane (3 mL) and treated with trifluoroacetic acid (1 mL). After stirring at room temperature for 4 h, the mixture was diluted with ether and stirred. The resulting white solid was collected by filtration to provide the title product as a white solid (201 mg, 87%): NMR ($DMSO-d_6$) δ 9.39 (bs, 2H), 9.19 (bs, 2H), 7.87 (s, 4H), 7.79 (t, 1H), 7.32 (m, 5H), 5.03 (3H), 4.40 (m, 2H), 3.90 (m, 1H), 3.65 (2s, 3H), 2.95 and 2.82 (4s, 3H), 3.6-2.8 (4H); mass spec (ESI) m/z 496.3 ($M+H^+$, 100%).

30

Example 701

Methyl N^2 -n-butyloxycarbonyl- N^3 -[3-(4-amidinophenyl)isoxazol-5-yl acetyl]-L-2,3-diaminopropionate TFA salt.

35 Part A. Preparation of Methyl 3-(4-cyanophenyl)isoxazol-5-yl acetate

-200-

To a suspension of methyl 3-(4-cyanophenyl)-(5R,S)-isoxazolin-5-yl acetate (5.28 g, 21.62 mmol) in chloroform (150 mL) were added *N*-bromosuccinimide (4.23 g, 23.78 mmol) and AIBN (100 mg) and the mixture was 5 refluxed. Small amounts of AIBN (100 mg - 200 mg) were added at one hour intervals until TLC showed a complete reaction. Potassium acetate (17.3 g) and acetic acid (6.5 mL) were added and the reaction mixture was refluxed for 1 hour, cooled, then poured into 1N NaOH 10 (325 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 100 mL). The organic layers were combined and washed with sat. NaCl, dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel 15 (15% to 35% EtOAc in Hexane) to yield 2.2 g (42%) of an off-white solid as product; ¹H NMR (300 MHz, CDCl₃) δ 7.93 (dd, 2H), 7.76 (dd, 2H), 6.67 (s, 1H), 3.92 (s, 2H), 3.8 (s, 3H).

20 Part B. Preparation of Methyl 3-(4-methoxyiminophenyl)isoxazo-5-yl acetate HCl salt.

A suspension of methyl 3-(4-cyanophenyl)isoxazo-5-yl acetate (2.19 g, 9.04 mmol) in 100 mL of anhydrous methanol was chilled in an ice bath and dry HCl gas was bubbled through the reaction mixture until a solution 25 was obtained. The total addition time was two hours. The reaction flask was sealed and the reaction mixture was allowed to warm to room temperature, with stirring, over a period of about 24 hrs. At this point, the methanolic solution was poured into 500 mL of anhydrous 30 ether, precipitating the product, and the resulting slurry was chilled to -25°C for 3 hours. The precipitate was filtered, washed with two 100 mL portions of chilled anhydrous ether, and suction dried under nitrogen to afford 2.3 g (82%) of the 35 hydrochloride salt; ¹H NMR (300 MHz, suspension in CDCl₃) δ 8.52 (d, J = 8.06 Hz, 2H), 8.03 (d, J = 8.4 Hz,

-201-

2H), 6.67 (s, 1H), 4.6 (s, 3H), 3.93 (s, 2H), 3.8 (s, 3H).

Part C. Preparation of Methyl 3-(4-amidinophenyl)isoxazo-5-yl acetate HCl salt.

5 A solution of methyl 3-(4-methoxyiminophenyl)isoxazo-5-yl acetate HCl salt (2.3 g, 7.4 mmol) in 50 mL of anhydrous methanol was chilled in an ice bath and 2M ammonia in methanol (18.5 mL, 37 mmol) was added. The reaction flask was sealed and the 10 reaction mixture was allowed to warm to room temperature, with stirring, over a period of 24 hrs. The amber solution was then concentrated in *vacuo* to give 2.2 g (quant. yield) of a yellow foam; ^1H NMR (300 MHz, d_6 -DMSO) δ 9.6-9.2 (b), 8.12 (d, J = 8.4 Hz, 2H), 15 7.97 (d, J = 8.4 Hz, 2H), 7.14 (s, 1H), 4.15 (s, 2H), 3.7 (s, 3H).

Part D. Preparation of Methyl 3-(4-N-Boc-amidinophenyl)isoxazo-5-yl acetate.

To a solution of methyl 3-(4-amidinophenyl)isoxazo-20 5-yl acetate HCl salt (2.2 g, 7.4 mmol) in 30 mL DMF cooled with an ice bath was added triethylamine (2.06 mL, 14.8 mmol) and di-*tert*-butyl dicarbonate (1.78 g, 8.14 mmol). The reaction mixture was warmed to room temperature and stirred for 64 hrs. The reaction 25 mixture was then partitioned between EtOAc and water. The aqueous layer was washed with EtOAc. The organic layers were combined and washed with water, sat. NaCl, dried over Na_2SO_4 , filtered, and concentrated in *vacuo*. The residue was chromatographed on silica gel (15% to 30 25% EtOAc in Hexane) to afford 1.45 g (54%) of product; ^1H NMR (300 MHz, CDCl_3) δ 7.96 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 8.4 Hz, 2H), 6.65 (s, 1H), 3.91 (s, 2H), 3.8 (s, 3H), 1.56 (s, 9H).

Part E. Preparation of 3-(4-N-Boc-amidinophenyl)isoxazo-5-yl acetic acid.

-202-

To a solution of methyl 3-(4-N-Boc-amidinophenyl)isoxazo-5-yl acetate (1.45 g, 4.03 mmol) in 30 mL of methanol was added a solution of lithium hydroxide monohydrate (0.195 g, 4.64 mmol) in water (5 mL). The mixture was stirred at room temperature for 16 hours. The reaction mixture was then concentrated *in vacuo* and the residue was diluted with water and the resulting mixture was cooled using an ice bath. 1N HCl was slowly added to a pH of 3 - 4 and the resulting acidic aqueous mixture was extracted repeatedly with EtOAc. The organic layers were combined and washed with sat. NaCl, dried over Na₂SO₄, filtered and concentrated *in vacuo* to yield 0.97 g (70%) of an off-white powdery solid as product; ¹H NMR (300 MHz, d₆-DMSO) δ 8.07 (d, J = 8.79 Hz, 2H), 7.97 (d, J = 8.4 Hz, 2H), 7.03 (s, 1H), 3.99 (s, 2H), 1.45 (s, 9H).

Part F. Preparation of Methyl N²-n-butyloxycarbonyl-N³-[3-(4-N-Boc-amidinophenyl)isoxazo-5-yl acetyl]-L-2,3-diaminopropionate.

To a solution of 3-(4-N-Boc-amidinophenyl)isoxazo-5-yl acetic acid (0.262 g, 0.76 mmol), methyl N²-carboxy-n-butyl-L-2,3-diaminopropionate HCl salt (0.193 g, 0.76 mmol), and TBTU (0.256 g, 0.8 mmol) in DMF (15 mL) was added triethylamine (0.45 mL, 3.23 mmol) and the resulting reaction mixture was allowed to stir at room temperature for 16 hours. The reaction mixture was partitioned between EtOAc and water. The water layer was washed twice with EtOAc. The organic layers were combined and washed with water, pH 4 buffer, 5% NaHCO₃, and sat. NaCl, dried over Na₂SO₄, filtered, and evaporated *in vacuo*. The residue was chromatographed on silica gel (100% EtOAc) to yield 0.315 g (76%) of a slightly amber foam; ¹H NMR (300 MHz, CDCl₃) δ 7.93 (d, J = 8.42 Hz, 2H), 7.83 (d, J = 8.42 Hz, 2H), 6.6 (s, 1H), 6.57 (bm, 1H), 5.66 (bm, 1H), 4.45 (bm, 1H), 4.05

-203-

(m, 2H), 3.77 (s, 5H), 3.7 (m, 2H), 1.57 (s, 9H), 1.56 (m, 2H), 1.35 (m, 2H), 0.9 (t, J = 7.32 Hz, 3H).

Part G. Preparation of Methyl N²-n-butyloxycarbonyl-N³-

[3-(4-amidinophenyl)isoxazo-5-yl acetyl]-L-2,3-
5 diaminopropionate TFA salt.

A solution of methyl N²-carboxy-n-buty1-N³-[3-(4-N-Boc-amidinophenyl)isoxazo-5-yl acetyl]-L-2,3-diaminopropionate (0.215 g, 0.39 mmol) in 1:1 methylene chloride / trifluoroacetic acid (20 mL total) was
10 stirred at room temperature for 16 hours. The reaction mixture was then concentrated *in vacuo* and the residue chromatographed on silica gel (10% to 30% methanol in chloroform) to yield 0.11 g (50%) of a white solid; ¹H NMR (300 MHz, d₆-DMSO) δ 9.4 (bs, 2H), 9.15 (bs, 2H),
15 8.45 (t, 1H), 8.11 (d, J = 8.42 Hz, 2H), 7.94 (d, J = 8.42 Hz, 2H), 7.53 (d, J = 8.06 Hz, 1H), 7.01 (s, 1H), 4.21 (m, 1H), 3.95 (t, 2H), 3.81 (s, 2H), 3.62 (s, 3H), 3.55 (m, 1H), 3.34 (m, 1H), 1.5 (m, 2H), 1.3 (m, 2H), 0.87 (t, J = 7.32 Hz, 3H); Mass Spectrum (ESI, e/z, 20 relative abundance) 446.3, (M+H)⁺, 100%.

Example 829

Methyl N²-n-butyloxycarbonyl-N³-[5-(4-formamidinophenyl)isoxazolin-3-yl acetyl]-L-(2S)-2,3-diaminopropionate

25

Part A: t-Butyl [5-(4-cyanophenyl)isoxazolin-3-ylacetate:

Cycloaddition of 4-cyanophenylethylene (MP&D
30 chemical Co.) and tert-butylformyl oxime was carried out following the procedure of Gree et. al. (Bioorganic & Medicinal Chemistry letters 1994, 253) to provide the desired isoxazoline in 72% yield. ¹HNMR(CDCl₃) δ: 1.40 (s, 9H), 3.00 (dd, J = 8.3 and 17Hz, 1H), 3.35 (dd(AB) J = 18 and 8.3 Hz, 2H), 3.48 (m, 1H), 5.60 (dd, J = 9 and 4.5 Hz, 1H), 7.47 (d, J = 8Hz, 2H), 7.65 (d, J = 8 Hz,

-204-

2H); IR 2235, 1718, 1610 cm^{-1} . Mass spectrum m/z 287 (M+H, 100).

Part B: [5-(4-cyanophenyl)isoxazolin-3-yl] acetic acid:

Hydrolysis of the compound of Ex. 829, Part A with 5 excess TFA in dichloromethane afforded the acid in 90% yield. ^1H NMR (CDCl_3) δ 3.00 (dd, J = 8 and 17.2 Hz, 1H), 3.55 (s, 2H), 3.59 (m, 1H), 5.66 (dd, J = 8 and 11Hz, 1H), 7.45 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.0 Hz, 2H); IR(KBr) 3325, 2235, 1718, 1605 cm^{-1} ; Mass spectrum m/z 10 231 (M+H, 100).

Part C: Methyl [5-(4-Boc-amidinophenyl)isoxazolin-3-yl] acetate: The compound of Ex. 829, Part B compound was

then subjected to the standard Pinner reaction 15 conditions described in Ex. 275, Part D to afford an amidino compound, which, without purification, was subjected to treatment with di-tert-butyldicarbonate in dioxane/water (9:1) and excess triethylamine to afford the desired compound in 28% yield. ^1H NMR (CDCl_3) δ 1.54 (s, 9H), 2.98 (dd, J = 8 and 17 Hz, 1H), 3.49 (s, 2H), 20 3.53 (m, 1H), 3.71 (s, 3H), 5.63 (dd, J = 8 & 11.4Hz, 1H), 7.38 (d, 8.2Hz, 2H), 7.82 ((d, 8.2Hz, 2H); Mass spectrum m/z 362 (M+H, 8), 306 (18), 262 (M+H-Boc, 100).

Part D: [5-(4-Boc-amidinophenyl)isoxazolin-3-yl]acetic acid: Hydrolysis of the ester using standard LiOH

25 conditions afforded the desired acid in 5% yield. ^1H NMR (CDCl_3) δ 1.54 (s, 9H), 3.00 (dd, J = 8 and 17 Hz, 1H), 3.51 (s, 2H), 3.53 (m, 1H), 5.63 (dd, J = 8 & 11.4Hz, 1H), 7.38 (d, 8.2Hz, 2H), 7.82 ((d, 8.2Hz, 2H); Mass spectrum m/z 348 (M+H, 12), 248 (M+H-Boc, 100).

30 Part E: Methyl N²-n-butyloxycarbonyl-N³-[5-(4-amidino phenyl)isoxazolin-3-yl]-acetyl]-S-2,3-diaminopropionate trifluoroacetate: The compound of Ex. 829, Part D was

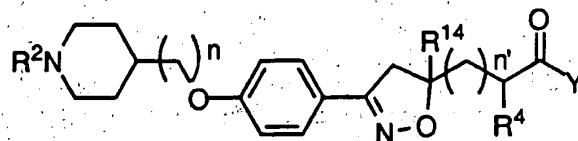
coupled with methyl-(S)-N²-n-butyloxycarbonyl-2,3-diaminopropionate following the procedure described in 35 Ex. 275, Part C to give the Boc protected intermediate in 80% yield. ^1H NMR (CDCl_3) δ 0.89 (t, 3H), 1.32 (m, 2H),

-205-

1.53 (s, 9H), 1.17 (m, 2H), 2.95 (dd, $J = 8$ and 17 Hz, 1H), 3.33 (s, 2H), 3.46 (m, 1H), 3.60 (m, 2H), 3.73 (s, 3H), 4.00 (m, 2H), 4.31 (m, 1H), 5.60 (dd, $J = 8$ & 11.4Hz, 1H), 5.70 (bd, 1H), 6.70 (broad, 1H), 7.33 (d, 8.2Hz, 2H), 7.89 ((d, 8.2Hz, 2H); Mass spectrum m/z 534 (M+H, 30), 434 (M+H-Boc, 100). Deprotection by treatment of the above Boc-amidine with excess TFA in dichloromethane provided the title compound as the TFA salt. ^1H NMR(CDCl₃/DMSO-d₆) δ 1.88 (t, 3H), 1.30 (m, 2H), 1.53 (m, 2H), 3.00 (dd, $J = 8$ and 17 Hz, 1H), 3.32 (s, 2H), 3.40-3.63 (m, 3H), 3.63 (d, 3H), 3.98 (t, 2H), 4.29 (m, 1H), 5.60 (dd, $J = 8$ & 11Hz, 1H), 6.80 (d, 1H), 7.50 (d, $J = 8$ Hz, 2H), 7.80 (d, $J = 8.2$ Hz, 2H), 8.03 (broad s, 1H), 9.05 (broad s, 2H); IR(KBr): 3388, 1718, 1664, 1620, 1528, 1456, 1436, 1384, 1366, 1280, 1254, 1168, 1144, 1074, 980, 882, 778 cm⁻¹; Mass spectrum(ES) m/z 448 (M+H, 100)

20 Using the above methods and variations thereof known in the art of organic synthesis, the additional examples in Tables 1-2, 2A-2D, 3-5 can be prepared.

Table 1



(V)

Ex. No.	R ²	R ⁴	Y	n	R ¹⁴	n'
1	H	H	OH	2	H	0
2	H	NHSO ₂ nC ₄ H ₉	OH	2	H	0
3	H	NHSO ₂ CH ₂ Ph	OH	2	H	0
4	H	NHCO ₂ CH ₂ Ph	OH	2	H	0
5	H	NHCO ₂ nC ₄ H ₉	OH	2	H	0
6	H	H	OH	1	H	1
7	H	H	OH	1	H	0
8	H	H	OH	2	H	1
9	H	NHSO ₂ nC ₄ H ₉	OH	1	H	1
10	H	NHSO ₂ CH ₂ Ph	OH	1	H	1
11	H	NHCO ₂ CH ₂ Ph	OH	1	H	1
12	H	NHCO ₂ nC ₄ H ₉	OH	1	H	1
13	H	NHSO ₂ nC ₄ H ₉	OMe	2	H	0
14	H	NHCO ₂ CH ₂ Ph	OMe	2	H	0
15	H	NHSO ₂ nC ₄ H ₉	OMe	1	H	1
16	H	NHCO ₂ CH ₂ Ph	OMe	1	H	1
17	H	NHSO ₂ nC ₄ H ₉	OEt	2	H	0
18	H	NHCO ₂ CH ₂ Ph	OEt	2	H	0
19	H	NHSO ₂ nC ₄ H ₉	OEt	1	H	1
20	H	NHCO ₂ CH ₂ Ph	OEt	1	H	1
21	Boc	NHSO ₂ nC ₄ H ₉	OH	2	H	0
22	Boc	NHCO ₂ CH ₂ Ph	OH	2	H	0
23	Boc	NHSO ₂ nC ₄ H ₉	OH	1	H	1
24	Boc	NHCO ₂ CH ₂ Ph	OH	1	H	1
25	Cbz	NHSO ₂ nC ₄ H ₉	OH	2	H	0
26	Cbz	NHCO ₂ CH ₂ Ph	OH	2	H	0
27	Cbz	NHSO ₂ nC ₄ H ₉	OH	1	H	1

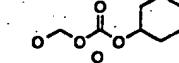
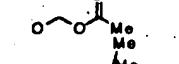
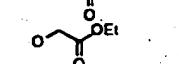
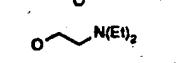
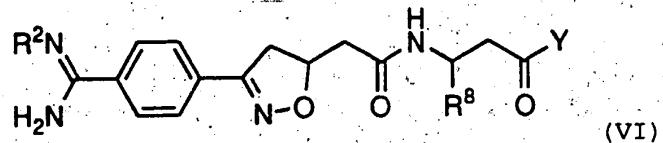
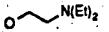
Ex. No.	R ²	R ⁴	Y	n	R ¹⁴	n'
28	Cbz	NHCO ₂ CH ₂ Ph	OH	1	H	1
29	H	NHSO ₂ nC ₄ H ₉		2	H	0
30	H	NHSO ₂ nC ₄ H ₉		2	H	0
31	H	NHSO ₂ nC ₄ H ₉		2	H	0
32	H	NHSO ₂ nC ₄ H ₉		2	H	0
31	H	NHSO ₂ nC ₄ H ₉		2	H	0
33	H	H	OH	2	CO ₂ Me	0
34	H	H	OMe	2	H	0
35	H	NHSO ₂ CH ₂ Ph	OMe	2	H	0
36	H	NHCO _n C ₄ H ₉	OMe	2	H	0
37	H	H	OMe	1	H	1
38	H	H	OMe	1	H	0
39	H	H	OMe	2	H	1
40	H	NHSO ₂ CH ₂ Ph	OMe	1	H	1
41	H	NHCO _n C ₄ H ₉	OMe	1	H	1
42	H	H	OMe	2	CO ₂ Me	0

Table 2

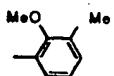
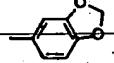
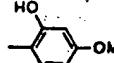
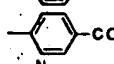
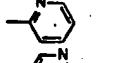
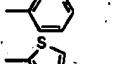
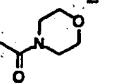
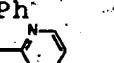
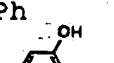
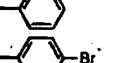
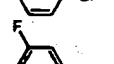
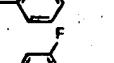
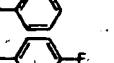
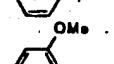


Example Number	R ²	R ⁸	Y	MS (M+H) ⁺
43	H	Ph	OH	412
44	H	-C ₆ H ₄ -Br	OH	
45	H	-C ₆ H ₄ -F	OH	
46	H	-C ₆ H ₄ -F	OH	
47	H	-C ₆ H ₄ -F	OH	
48	H	-C ₆ H ₄ -OMe	OH	
49	H	-C ₆ H ₄ -OEt	OH	
50	H	-C ₆ H ₄ -OPh	OH	
51	H	-C ₆ H ₄ -OPh	OH	
52	H	-C ₆ H ₄ -Cl	OH	
53	H	-C ₆ H ₄ -CN	OH	
54	H	-C ₆ H ₄ -CF ₃	OH	
55	H	-C ₆ H ₄ -CF ₃	OH	
56	H	-C ₆ H ₄ -CF ₃	OH	
57	H	-C ₆ H ₄ -Cl	OH	
58	H	-C ₆ H ₄ -Cl	OH	
59	H	-C ₆ H ₄ -OMe	OH	
60	H	-C ₆ H ₄ -OMe	OH	

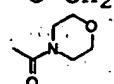
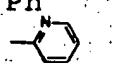
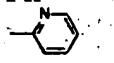
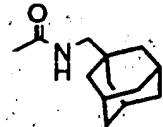
Example Number	R ²	R ⁸	Y	MS (M+H) ⁺
61	H		OH	
62	H		OH	
63	H		OH	
64	H		OH	
65	H		OH	
66	H		OH	
67	H		OH	
68	H		OH	
69	H	Et	OH	
70	H	n-Pr	OH	
71	H	-C≡CH	OH	
72	H	CO ₂ H	OH	
73	H	CH ₂ Ph	OH	
74	H	CH ₂ CH ₂ Ph	OH	
75	H	-C=CH ₂	OH	
76	H		OH	
80	Cbz	Ph	OH	
81	Cbz		OH	
82	Boc	Ph	OH	
83	Boc		OH	
84	H			
85	H			
86	H			
87	H			

Example Number	R ²	R ⁸	Y	MS (M+H) ⁺
88	H			
89	H		OMe	
90	H		OMe	
91	H		OMe	
92	H		OMe	
93	H		OMe	
94	H		OMe	
95	H		OMe	
96	H		OMe	
97	H		OMe	
98	H		OMe	
99	H		OMe	
100	H		OMe	
101	H		OMe	
102	H		OMe	
103	H		OMe	
104	H		OMe	
105	H		OMe	
106	H		OMe	

Example Number	R ²	R ⁸	Y	MS (M+H) ⁺
107	H		OMe	

108	H		OMe	
109	H		OMe	
110	H		OMe	
111	H		OMe	
112	H		OMe	
113	H		OMe	
114	H		OMe	
115	H	Et	OMe	361
116	H	<i>n</i> -Pr	OMe	
117	H	-C≡CH	OMe	
118	H	CO ₂ H	OMe	
119	H	CH ₂ Ph	OMe	423
120	H	CH ₂ CH ₂ Ph	OMe	437
121	H	-C=CH ₂	OMe	
122	H		OMe	
126	Cbz		OMe	
127	Cbz		OMe	
128	Boc		OMe	
129	Boc		OMe	
130	H	Ph	OEt	
131	H		OEt	
132	H		OEt	
133	H		OEt	
134	H		OEt	
135	H		OEt	
136	H		OEt	
137	H		OEt	

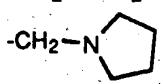
Example Number	R ²	R ⁸	Y	MS (M+H) ⁺
138	H		OEt	
139	H		OEt	
140	H		OEt	
141	H		OEt	
142	H		OEt	
143	H		OEt	
144	H		OEt	
145	H		OEt	
146	H		OEt	
147	H		OEt	
148	H		OEt	
149	H		OEt	
150	H		OEt	
151	H		OEt	
152	H		OEt	
153	H		OEt	
154	H		OEt	
Example Number	R ²	R ⁸	Y	MS (M+H) ⁺
155	H		OEt	
156	H	Et	OEt	
157	H	n-Pr	OEt	
158	H	-C≡CH	OEt	

159	H	CO ₂ H	OEt	
160	H	CH ₂ Ph	OEt	
161	H	CH ₂ CH ₂ Ph	OEt	
162	H	-C=CH ₂	OEt	
163	H		OEt	
164	H	CH ₂ N(Me)Ph	OEt	
165	H	CH ₂ NET ₂	OEt	
166	H	CH ₂ NMe ₂	OEt	
167	Cbz	Ph	OEt	
168	Cbz		OEt	
169	Boc	Ph	OEt	
170	Boc		OEt	
338	H	CO ₂ Me	OMe	mp 160°
339	H	CO ₂ Me	H	363
340	H	CONMe ₂	OMe	404
341	H		OMe	524
343	H	n-butyl	OH	
344	H	n-butyl	OMe	389
345	H	n-butyl	OEt	
346	H	isobutyl	OH	
347	H	isobutyl	OMe	389
348	H	isobutyl	OEt	403
349	H	CH ₂ SPh	OH	
350	H	CH ₂ SPh	OMe	455
351	H	CH ₂ SPh	OEt	
352	H	CH ₂ OPh	OH	
353	H	CH ₂ OPh	OMe	
354	H	CH ₂ OPh	OEt	
355	H	CH ₂ SO ₂ Ph	OH	
356	H	CH ₂ SO ₂ Ph	OMe	
357	H	CH ₂ SO ₂ Ph	OEt	
358	H	CH ₂ NHSO ₂ Ph	OH	

Example Number	R ²	R ⁸	Y	MS (M+H) ⁺
359	H	CH ₂ NHSO ₂ Ph	OMe	502
360	H	CH ₂ NHSO ₂ Ph	OEt	
361	H	CH ₂ NHSO ₂ n-Bu	OH	
362	H	CH ₂ NHSO ₂ n-Bu	OMe	482
363	H	CH ₂ NHSO ₂ n-Bu	OEt	
364	H	CH ₂ COOH	OH	377
365	H	CH ₂ COOMe	OMe	405
366	H	CH ₂ COOEt	OEt	
367	H	CH ₂ CH ₂ COOH	OH	
368	H	CH ₂ CH ₂ COOMe	OMe	419
369	H	CH ₂ CH ₂ COOEt	OEt	
370	H	CH ₂ NMe ₂	OH	
371	H	CH ₂ NMe ₂	OMe	390
372	H	CH ₂ NMe ₂	OEt	
434	BOC	-C(=O)NH-(CH ₂) ₂ C ₆ H ₅	OtBu	622
435	H	-C(=O)NH-(CH ₂) ₂ C ₆ H ₅	OH	466
439	H	-C(=O)OC ₂ H ₅	OEt	419
441	H		OH	484
446	H	(CH ₂) ₃ Ph	OMe	
447	H	CH ₂ - (2-pyr)	OMe	
448	H	(CH ₂) ₂ - (2-pyr)	OMe	
449	H	(CH ₂) ₂ - (3-pyr)	OMe	438
450	H	(CH ₂) ₂ - (4-pyr)	OMe	438
452	H	-C(=O)NH-(CH ₂) ₂ C ₆ H ₅	OMe	480
453	BOC	C(O)·N [N·CH ₂ Ph]	OMe	635
454	H	C(=O)N(CH ₃) - (CH ₂) ₂ C ₆ H ₅	OMe	
455	H	C(O)·N [N·CH ₂ Ph]	OMe	
456	H	i-hexyl	OEt	431

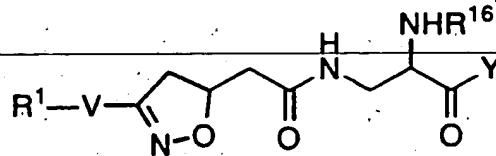
Example Number	R ²	R ⁸	Y	MS (M+H) ⁺
457	H	-C≡CSiMe ₃	OMe	429
458	H	-(CH ₂) ₂ -(3-pyr)	OH	424
459	H	-(CH ₂) ₂ -(2-pyr)	OH	424
460	H	-(CH ₂) ₃ -C ₆ H ₅	OH	437
461	H	-(CH ₂) ₃ -C ₆ H ₅	OMe	451
462	H		OEt	538
463	H		OH	510
464	H		OMe	492
465	H		OMe	492
466	H		OMe	510
467	H		OMe	510
468	H		OMe	462
469	H		OMe	448
587	H	-(CH ₂) ₃ -(4-pyr)	OH	424

-216-

Example Number	R ²	R ⁸	Y	MS. (M+H) ⁺
611	H	-CH ₂ NHSO ₂ NMe ₂	OMe	469
612	H	-CH ₂ -N 	OMe	416

-217-

Table 2A



Example Number	R ¹ -V	R ¹⁶	Y	MS (M+H) ⁺
275	4-amidinophenyl	H	OH	334
276	4-amidinophenyl	benzyloxycarbonyl	OH	468
277	4-amidinophenyl	t-butyloxycarbonyl	OH	
278	4-amidinophenyl	n-butyloxycarbonyl	OH	434
279	4-amidinophenyl	ethyloxycarbonyl	OH	
280	4-amidinophenyl	methyloxycarbonyl	OH	
290	4-amidinophenyl	phenylethylcarbonyl	OH	510
291	4-amidinophenyl	2,2-dimethyl- propylcarbonyl	OH	
292	4-amidinophenyl	n-pentylcarbonyl	OH	
293	4-amidinophenyl	n-butylcarbonyl	OH	
294	4-amidinophenyl	propionyl	OH	
295	4-amidinophenyl	acetyl	OH	
296	4-amidinophenyl	methylsulfonyl	OH	
297	4-amidinophenyl	ethylsulfonyl	OH	
298	4-amidinophenyl	n-butylsulfonyl	OH	
299	4-amidinophenyl	phenylsulfonyl	OH	
300	4-amidinophenyl	4-methylphenyl- sulfonyl	OH	488
301	4-amidinophenyl	benzylsulfonyl	OH	
302	4-amidinophenyl	2-pyridylcarbonyl	OH	
303	4-amidinophenyl	3-pyridylcarbonyl	OH	
304	4-amidinophenyl	4-pyridylcarbonyl	OH	
305	4-amidinophenyl	2-pyridylmethyl- carbonyl	OH	
306	4-amidinophenyl	3-pyridylmethyl- carbonyl	OH	

-218-

Example Number	R ¹ -V	R ¹⁶	Y	MS (M+H) ⁺
307	4-amidinophenyl	4-pyridylmethyl- carbonyl	OH	
308	4-amidinophenyl	2-pyridylmethoxy- carbonyl	OH	
309	4-amidinophenyl	3-pyridylmethoxy- carbonyl	OH	
310	4-amidinophenyl	4-pyridylmethoxy- carbonyl	OH	
311	4-amidinophenyl	H	OMe	
312	4-amidinophenyl	benzyloxycarbonyl	OMe	482
313	4-amidinophenyl	t-butyloxycarbonyl	OMe	
314	4-amidinophenyl	n-butyloxycarbonyl	OMe	448
315	4-amidinophenyl	ethyloxycarbonyl	OMe	
316	4-amidinophenyl	methyloxycarbonyl	OMe	
317	4-amidinophenyl	phenylethylcarbonyl	OMe	
318	4-amidinophenyl	2,2-dimethyl- propylcarbonyl	OMe	
319	4-amidinophenyl	n-pentylcarbonyl	OMe	
320	4-amidinophenyl	n-butylcarbonyl	OMe	
321	4-amidinophenyl	propionyl	OMe	
322	4-amidinophenyl	acetyl	OMe	
323	4-amidinophenyl	methylsulfonyl	OMe	426
324	4-amidinophenyl	ethylsulfonyl	OMe	440
325	4-amidinophenyl	n-butylsulfonyl	OMe	
326	4-amidinophenyl	phenylsulfonyl	OMe	488
327	4-amidinophenyl	4-methylphenyl- sulfonyl	OMe	502
328	4-amidinophenyl	benzylsulfonyl	OMe	502
329	4-amidinophenyl	2-pyridylcarbonyl	OMe	
330	4-amidinophenyl	3-pyridylcarbonyl	OMe	
331	4-amidinophenyl	4-pyridylcarbonyl	OMe	

-219-

Example Number	R ¹ -V	R ¹⁶	Y	MS. (M+H) ⁺
332	4-amidinophenyl	2-pyridylmethyl- carbonyl	OMe	
333	4-amidinophenyl	3-pyridylmethyl- carbonyl	OMe	
334	4-amidinophenyl	4-pyridylmethyl- carbonyl	OMe	
335	4-amidinophenyl	2-pyridylmethoxy- carbonyl	OMe	
336	4-amidinophenyl	3-pyridylmethoxy- carbonyl	OMe	
337	4-amidinophenyl	4-pyridylmethoxy- carbonyl	OMe	
374	4-piperidinylethyl	benzylcarbonyl	OMe	475
440	4-(BOCamidino)phenyl	benzyloxycarbonyl	OMe	582
442	4-(BOCamidino)phenyl	n-butyloxycarbonyl	OMe	594
443	4-amidinophenyl	1-naphthylsulfonyl	OMe	538
444	4-amidinophenyl	2-naphthylsulfonyl	OMe	538
445	4-amidinophenyl	styrylsulfonyl	OMe	514
451	4-piperidinylethyl	n-butyloxycarbonyl	OMe	441
471	4-amidinophenyl	4-butyloxyphenyl- sulfonyl	OMe	560
472	4-amidinophenyl	2-thienylsulfonyl	OMe	494
473	4-amidinophenyl	3-methylphenyl- sulfonyl	OMe	502
474	4-amidinophenyl	4-iodophenyl	OMe	614
475	4-amidinophenyl	3-trifluoromethyl- phenylsulfonyl	OMe	556
476	4-amidinophenyl	3-chlorophenyl- sulfonyl	OMe	522
477	4-amidinophenyl	2-methoxycarbonyl- phenylsulfonyl	OMe	546

-220-

Example Number	R ¹ -v	R ¹⁶	Y	MS (M+H) ⁺
478	4-amidinophenyl	2,4,6-trimethyl- phenylsulfonyl	OMe	530
479	4-amidinophenyl	2-chlorophenyl- sulfonyl	OMe	522
480	4-amidinophenyl	2-trifluoromethyl- phenylsulfonyl	OMe	556
481	4-amidinophenyl	4-trifluoromethyl- phenylsulfonyl	OMe	556
482	4-amidinophenyl	2-fluorophenyl- sulfonyl	OMe	506
483	4-amidinophenyl	4-fluorophenyl- sulfonyl	OMe	506
484	4-amidinophenyl	4-methoxyphenyl- sulfonyl	OMe	518
485	4-amidinophenyl	2,3,5,6-tetramethyl- phenylsulfonyl	OMe	544
486	4-amidinophenyl	4-cyanophenyl- sulfonyl	OMe	513
487	4-amidinophenyl	4-chlorophenyl- sulfonyl	OMe	522
488	4-amidinophenyl	4-ethylphenyl- sulfonyl	OMe	516
489	4-amidinophenyl	4-propylphenyl- sulfonyl	OMe	530
490	4-amidinophenyl	n-propylsulfonyl	OMe	454
491	4-amidinophenyl	2-phenylethyl- sulfonyl	OMe	516
492	4-amidinophenyl	4-isopropylphenyl- sulfonyl	OMe	530
493	4-amidinophenyl	3-phenylpropyl- sulfonyl	OMe	530
494	4-amidinophenyl	3-pyridylsulfonyl	OMe	489

-221-

Example Number	R ¹ -Y	R ¹⁶	Y	MS (M+H) ⁺
495	4-amidinophenyl	2-pyridylsulfonyl	OMe	489
496	4-amidinophenyl	2,2-diphenyl-1-ethenylsulfonyl	OMe	590
497	4-amidinophenyl	2-pyrimidinyl-sulfonyl	OMe	
498	4-amidinophenyl	4-methyl-2-pyrimidinylsulfonyl	OMe	
499	4-amidinophenyl	4,6-dimethyl-2-pyrimidinylsulfonyl	OMe	
500	4-amidinophenyl	1,2,4-triazol-3-ylsulfonyl	OMe	
501	4-amidinophenyl	1-methyl-1,3,4-triazol-5-ylsulfonyl	OMe	
502	4-amidinophenyl	3,5-dimethyl-4-pyrazolylsulfonyl	OMe	
503	4-amidinophenyl	1-phenyl-4-pyrazolylsulfonyl	OMe	
504	4-amidinophenyl	n-butylaminosulfonyl	OMe	483
505	4-amidinophenyl	i-butylaminosulfonyl	OMe	483
506	4-amidinophenyl	t-butylaminosulfonyl	OMe	483
507	4-amidinophenyl	i-propylamino-sulfonyl	OMe	469
508	4-amidinophenyl	cyclohexylamino-sulfonyl	OMe	509
509	4-amidinophenyl	phenylaminosulfonyl	OMe	503
510	4-amidinophenyl	benzylaminosulfonyl	OMe	517
511	4-amidinophenyl	dimethylamino-sulfonyl	OMe	455
512	4-amidino-2-fluoro-phenyl	3-methylphenyl-sulfonyl	OMe	520
513	2-amidino-5-pyridyl	n-butyloxycarbonyl	OMe	449

-222-

Example Number	R ¹ -V	R ¹⁶	Y	MS (M+H) ⁺
514	2-amidino-5-pyridyl	3-methylphenyl- sulfonyl	OMe	503
515	3-amidino-6-pyridyl	n-butyloxycarbonyl	OMe	449
516	3-amidino-6-pyridyl	3-methylphenyl- sulfonyl	OMe	503
517	4-amidinophenyl	phenylaminocarbonyl	OMe	467
518	4-amidinophenyl	4-fluorophenylamino- carbonyl	OMe	485
519	4-amidinophenyl	1-naphthylamino- carbonyl	OMe	517
520	4-amidinophenyl	benzylaminocarbonyl	OMe	
521	4-amidinophenyl	n-butyloxycarbonyl	OMe	435
522	4-amidinophenyl	4-ethylphenyl- carbonyl	OMe	480
523	4-amidinophenyl	biphenylcarbonyl	OMe	528
524	4-amidinophenyl	2-naphthylcarbonyl	OMe	502
525	4-amidinophenyl	(2-chlorophenyl)- methoxycarbonyl	OMe	516
526	4-amidinophenyl	(2-chlorophenyl)- methoxycarbonyl	OH	502
527	4-amidinophenyl	(2-bromophenyl)- methoxycarbonyl	OMe	562
528	4-amidinophenyl	(2-bromophenyl)- methoxycarbonyl	OH	548
529	4-amidinophenyl	n-hexyloxycarbonyl	OMe	476
530	4-amidinophenyl	n-hexyloxycarbonyl	OH	460
531	4-amidinophenyl	isobutyloxycarbonyl	OMe	448
532	4-amidinophenyl	isobutyloxycarbonyl	OH	434
533	4-amidinophenyl	2-cyclopropylethoxy- carbonyl	OMe	460
534	4-amidinophenyl	2-cyclopropylethoxy- carbonyl	OH	446

-223-

Example Number	R ¹ -V	R ¹⁶	Y	MS (M+H) ⁺
535	4-amidinophenyl	2-cyclopentylethoxy- carbonyl	OMe	488
536	4-amidinophenyl	2-cyclopentylethoxy- carbonyl	OH	474
537	4-amidinophenyl	4,4,4-trifluoro- butyloxycarbonyl	OMe	502
538	4-amidinophenyl	4,4,4-trifluoro- butyloxycarbonyl	OH	488
539	4-amidinophenyl	n-propylsulfonyl	OMe	
540	4-amidinophenyl	2-methylphenyl- sulfonyl	OMe	
541	4-amidinophenyl	4-chloro-2,5-dimethyl- phenylsulfonyl	OMe	550
542	4-amidinophenyl	2,3-dichlorophenyl- sulfonyl	OMe	556
543	4-amidinophenyl	2-bromophenyl- sulfonyl	OMe	568
544	4-amidinophenyl	3-bromophenyl- sulfonyl	OMe	568
545	4-amidinophenyl	4-bromophenyl- sulfonyl	OMe	568
546	4-amidinophenyl	biphenylsulfonyl	OMe	564
547	4-amidinophenyl	5-chloro-1,3- dimethyl-4-pyrazolyl	OMe	540
548	4-amidinophenyl	3-bromo-2- thienylsulfonyl	OMe	574
549	4-amidinophenyl	5-bromo-2- thienylsulfonyl	OMe	574
550	4-amidinophenyl	5-[1-methyl-5- trifluoromethyl-3- pyrazolyl]-2- thienylsulfonyl	OMe	642

-224-

Example Number	R ¹ -V	R ¹⁶	Y	MS (M+H) ⁺
551	4-amidinophenyl	5-(3-isoxazolyl)-2-thienylsulfonyl	OMe	561
552	4-amidinophenyl	5-(2-pyridinyl)-2-thienylsulfonyl	OMe	571
553	4-amidinophenyl	4-methyl-2-methylcarbonylamino-5-thiazolylsulfonyl	OMe	566
554	4-amidinophenyl	2-benzothienyl-sulfonyl	OMe	628
555	4-amidinophenyl	2-benzothienyl-sulfonyl	OMe	544
556	4-amidinophenyl	3-methyl-2-benzothienylsulfonyl	OMe	558
557	4-amidinophenyl	8-quinolinylsulfonyl	OMe	
558	4-amidinophenyl	8-quinolinylsulfonyl	OH	
559	4-amidinophenyl	2,1,3-benzo-thiadiazol-4-ylsulfonyl	OMe	
560	4-amidinophenyl	2,1,3-benzo-thiadiazol-4-ylsulfonyl	OH	
561	4-amidinophenyl	4-N,N-dimethylamino-1-naphthylsulfonyl	OMe	
562	4-amidinophenyl	4-N,N-dimethylamino-1-naphthylsulfonyl	OH	
563	4-amidinophenyl	2,1,3-benzoxadiazol-4-ylsulfonyl	OMe	
564	4-amidinophenyl	2,1,3-benzoxadiazol-4-ylsulfonyl	OH	
565	4-amidinophenyl	2,2,5,7,8-pentamethyl-3,4-dihydro-2Hbenzo-pyran-6-ylsulfonyl	OMe	

-225-

Example Number	R ¹ -V	R ¹⁶	Y	MS (M+H) ⁺
566	4-amidinophenyl	2,2,5,7,8-pentamethyl 3,4-dihydro-2Hbenzo- pyran-6-ylsulfonyl	OH	
567	4-N-methylamidino phenyl	3-methylphenylsulfonyl	OMe	
568	4-N-ethylamidino phenyl	3-methylphenylsulfonyl	OMe	530
569	4-N-n-propylamidino phenyl	3-methylphenylsulfonyl	OMe	
570	4-N-benzylamidino phenyl	3-methylphenylsulfonyl	OMe	
571	4-N-n-butylamidino phenyl	3-methylphenylsulfonyl	OMe	
572	4-N-methylamidino phenyl	3-methylphenylsulfonyl	OH	
573	4-N-ethylamidino phenyl	3-methylphenylsulfonyl	OH	
574	4-N-n-propylamidino phenyl	3-methylphenylsulfonyl	OH	
575	4-N-benzylamidino phenyl	3-methylphenylsulfonyl	OH	
576	4-N-n-butylamidino phenyl	3-methylphenylsulfonyl	OH	
577	4-N-methylamidino- phenyl	n-butyloxycarbonyl	OMe	
578	4-N-ethylamidinophenyl	n-butyloxycarbonyl	OMe	
579	4-N-npropylamidino- phenyl	n-butyloxycarbonyl	OMe	
580	4-N-n-butylamidino- phenyl	n-butyloxycarbonyl	OMe	504
581	4-N-benzylamidino- phenyl	n-butyloxycarbonyl	OMe	

Example Number	R ¹ -V	R ¹⁶	Y	MS (M+H) ⁺
582	4-N-methylamidino- phenyl	n-butyloxycarbonyl	OH	
583	4-N-ethylamidino- phenyl	n-butyloxycarbonyl	OH	
584	4-N-n-propylamidino- phenyl	n-butyloxycarbonyl	OH	
585	4-N-n-butylamidino- phenyl	n-butyloxycarbonyl	OH	
586	4-N-benzylamidino- phenyl	n-butyloxycarbonyl	OH	
589	4-(acetoxyamidino)- phenyl	n-butyloxycarbonyl	OMe	
590	4-(acetoxyamidino)- phenyl	n-butyloxycarbonyl	OH	
591	4-(acetoxyamidino)- phenyl	isobutyloxycarbonyl	OMe	
592	4-(acetoxyamidino)- phenyl	isobutyloxycarbonyl	OH	
593	4-(acetoxyamidino)- phenyl	cyclopropylethoxy- carbonyl	OMe	
594	4-(acetoxyamidino)- phenyl	cyclopropylethoxy- carbonyl	OH	
595	4-(acetoxyamidino)- phenyl	benzyloxycarbonyl	OMe	
596	4-(acetoxyamidino)- phenyl	benzyloxycarbonyl	OH	
597	4-(acetoxyamidino)- phenyl	4-methylphenylsulfonyl	OMe	
598	4-(acetoxyamidino)- phenyl	4-methylphenylsulfonyl	OH	

Example Number	R ¹ -V	R ¹⁶	Y	MS (M+H) ⁺
599	4-(acetoxyamidino)-phenyl	3-methylphenylsulfonyl	OMe	
600	4-(acetoxyamidino)-phenyl	3-methylphenylsulfonyl	OH	
601	4-guanidinophenyl	n-butyloxycarbonyl	OH	
602	4-guanidinophenyl	n-butyloxycarbonyl	OMe	463
603	4-guanidinophenyl	benzyloxycarbonyl	OH	
604	4-guanidinophenyl	benzyloxycarbonyl	OMe	
605	4-guanidinophenyl	4-methylphenylsulfonyl	OH	
606	4-guanidinophenyl	4-methylphenylsulfonyl	OMe	
607	4-guanidinophenyl	3-methylphenylsulfonyl	OH	
608	4-guanidinophenyl	3-methylphenylsulfonyl	OMe	
609	4-guanidinophenyl	n-butylsulfonyl	OH	
610	4-guanidinophenyl	n-butylsulfonyl	OMe	
613	4-amidino-2-fluoro-phenyl	n-butyloxycarbonyl	OMe	466
614	4-piperidinyl	n-butyloxycarbonyl	OMe	412
615	4-piperidinylmethyl	n-butyloxycarbonyl	OMe	426
616	4-piperidinylpropyl	n-butyloxycarbonyl	OMe	454
617	4-quanidinophenyl	n-butyloxycarbonyl	OH	449
618	4-amidinophenylmethyl	benzyloxycarbonyl	OMe	
619	4-amidinophenylmethyl	benzyloxycarbonyl	OH	
220	4-amidinophenylmethyl	n-butyloxycarbonyl	OMe	
621	4-amidinophenylmethyl	n-butyloxycarbonyl	OH	
622	4-amidinophenylmethyl	cyclopropylethoxy carbonyl	OMe	
623	4-amidinophenylmethyl	cyclopropylethoxy carbonyl	OH	
624	4-amidinophenylmethyl	4-methylphenylsulfonyl	OMe	
625	4-amidinophenylmethyl	4-methylphenylsulfonyl	OH	
626	4-amidinophenylmethyl	3-methylphenylsulfonyl	OMe	
627	4-amidinophenylmethyl	3-methylphenylsulfonyl	OH	

-228-

Example Number	R ¹ -V	R ¹⁶	Y	MS (M+H) ⁺
628	4-amidinophenylmethyl	n-butylsulfonyl	OMe	
629	4-amidinophenylmethyl	n-butylsulfonyl	OH	
630	4-amidinophenylmethoxy	benzyloxycarbonyl	OMe	
631	4-amidinophenylmethoxy	benzyloxycarbonyl	OH	
632	4-amidinophenylmethoxy	n-butyloxycarbonyl	OMe	
633	4-amidinophenylmethoxy	n-butyloxycarbonyl	OH	
634	4-amidinophenylmethoxy	cyclopropylethoxy carbonyl	OMe	
635	4-amidinophenylmethoxy	cyclopropylethoxy carbonyl	OH	
636	4-amidinophenylmethoxy	4-methylphenylsulfonyl	OMe	
637	4-amidinophenylmethoxy	4-methylphenylsulfonyl	OH	
638	4-amidinophenylmethoxy	3-methylphenylsulfonyl	OMe	
639	4-amidinophenylmethoxy	3-methylphenylsulfonyl	OH	
640	4-amidinophenylmethoxy	n-butylsulfonyl	OMe	
641	4-amidinophenylmethoxy	n-butylsulfonyl	OH	
801	4-amidinophenoxyethyl	benzyloxycarbonyl	OMe	
802	4-amidinophenoxyethyl	benzyloxycarbonyl	OH	
803	4-amidinophenoxyethyl	n-butyloxycarbonyl	OMe	
804	4-amidinophenoxyethyl	n-butyloxycarbonyl	OH	
805	4-amidinophenoxyethyl	cyclopropylethoxy carbonyl	OMe	
806	4-amidinophenoxyethyl	cyclopropylethoxy carbonyl	OH	
807	4-amidinophenoxyethyl	4-methylphenylsulfonyl	OMe	
808	4-amidinophenoxyethyl	4-methylphenylsulfonyl	OH	
809	4-amidinophenoxyethyl	3-methylphenylsulfonyl	OMe	
810	4-amidinophenoxyethyl	3-methylphenylsulfonyl	OH	
811	4-amidinophenoxyethyl	n-butylsulfonyl	OMe	
812	4-amidinophenoxyethyl	n-butylsulfonyl	OH	
813	4-amidinophenoxy	benzyloxycarbonyl	OMe	
814	4-amidinophenoxy	benzyloxycarbonyl	OH	

-229-

Example Number	R ¹ -V	R ¹⁶	Y	MS (M+H) ⁺
815	4-amidinophenoxy	n-butyloxycarbonyl	OMe	
816				
817	4-amidinophenoxy	n-butyloxycarbonyl	OH	
818	4-amidinophenoxy	cyclopropylethoxy carbonyl	OHe	
819	4-amidinophenoxy	cyclopropylethoxy carbonyl	OH	
820	4-amidinophenoxy	4-methylphenylsulfonyl	OMe	
821	4-amidinophenoxy	4-methylphenylsulfonyl	OH	
822	4-amidinophenoxy	3-methylphenylsulfonyl	OMe	
823	4-amidinophenoxy	3-methylphenylsulfonyl	OH	
824	4-amidinophenoxy	n-butylsulfonyl	OMe	
825	4-amidinophenoxy	n-butylsulfonyl	OH	
826	4-amidinophenethyl	benzyloxycarbonyl	OMe	
827	4-amidinophenethyl	benzyloxycarbonyl	OH	
828	4-amidinophenethyl	n-butyloxycarbonyl	OMe	
829	4-amidinophenethyl	n-butyloxycarbonyl	OH	
830	4-amidinophenethyl	cyclopropylethoxy carbonyl	OMe	
831	4-amidinophenethyl	cyclopropylethoxy carbonyl	OH	
832	4-amidinophenethyl	4-methylphenylsulfonyl	OMe	
833	4-amidinophenethyl	4-methylphenylsulfonyl	OH	
834	4-amidinophenethyl	3-methylphenylsulfonyl	OMe	
835	4-amidinophenethyl	3-methylphenylsulfonyl	OH	
836	4-amidinophenethyl	n-butylsulfonyl	OMe	
837	4-amidinophenethyl	n-butylsulfonyl	OH	
838	N-(4-amidinophenyl) aminomethyl	benzyloxycarbonyl	OMe	
839	N-(4-amidinophenyl) aminomethyl	benzyloxycarbonyl	OH	

-230-

Example Number	R ¹ -V	R ¹⁶	Y	MS (M+H) ⁺
840	N-(4-amidinophenyl) aminomethyl	n-butyloxycarbonyl	OMe	
841	N-(4-amidinophenyl) aminomethyl	n-butyloxycarbonyl	OH	
842	N-(4-amidinophenyl) aminomethyl	cyclopropylethoxy carbonyl	OH	
843	N-(4-amidinophenyl) aminomethyl	4-methylphenylsulfonyl	OMe	
844	N-(4-amidinophenyl) aminomethyl	4-methylphenylsulfonyl	OH	
845	N-(4-amidinophenyl) aminomethyl	3-methylphenylsulfonyl	OMe	
846	N-(4-amidinophenyl) aminomethyl	3-methylphenylsulfonyl	OH	
847	N-(4-amidinophenyl) aminomethyl	n-butylsulfonyl	OMe	
848	N-(4-amidinophenyl) aminomethyl	n-butylsulfonyl	OH	
849	4-amidinophenyl methylamino	benzyloxycarbonyl	OMe	
850	4-amidinophenyl methylamino	benzyloxycarbonyl	OH	
851	4-amidinophenyl methylamino	n-butyloxycarbonyl	OMe	
852	4-amidinophenyl methylamino	n-butyloxycarbonyl	OH	
853	4-amidinophenyl methylamino	cyclopropylethoxy carbonyl	OMe	
854	4-amidinophenyl methylamino	cyclopropylethoxy carbonyl	OH	
855	4-amidinophenyl methylamino	4-methylphenylsulfonyl	OMe	

-231-

Example Number	R ¹ -V	R ¹⁶	Y	MS (M+H) ⁺
856	4-amidinophenyl methylamino	4-methylphenylsulfonyl	OH	
857	4-amidinophenyl methylamino	3-methylphenylsulfonyl	OMe	
858	4-amidinophenyl methylamino	n-butylsulfonyl	OMe	
859	4-amidinophenyl methylamino	n-butylsulfonyl	OH	
860	N-(4-amidinophenyl) aminocarbonyl	benzyloxycarbonyl	OMe	
861	N-(4-amidinophenyl) aminocarbonyl	benzyloxycarbonyl	OH	
862	N-(4-amidinophenyl) aminocarbonyl	n-butyloxycarbonyl	OMe	
863	N-(4-amidinophenyl) aminocarbonyl	n-butyloxycarbonyl	OH	
864	N-(4-amidinophenyl) aminocarbonyl	cyclopropylethoxy carbonyl	OMe	
865	N-(4-amidinophenyl) aminocarbonyl	cyclopropylethoxy carbonyl	OH	
866	N-(4-amidinophenyl) aminocarbonyl	4-methylphenylsulfonyl	OMe	
867	N-(4-amidinophenyl) aminocarbonyl	4-methylphenylsulfonyl	OH	
868	N-(4-amidinophenyl) aminocarbonyl	3-methylphenylsulfonyl	OMe	
869	N-(4-amidinophenyl) aminocarbonyl	3-methylphenylsulfonyl	OH	
870	N-(4-amidinophenyl) aminocarbonyl	n-butylsulfonyl	OMe	
871	N-(4-amidinophenyl) aminocarbonyl	n-butylsulfonyl	OH	

-232-

Example Number	R ¹ -V	R ¹⁶	Y	MS (M+H) ⁺
872	4-amidinophenyl carbonylamino	benzyloxycarbonyl	OMe	
873	4-amidinophenyl carbonylamino	benzyloxycarbonyl	OH	
874	4-amidinophenyl carbonylamino	n-butyloxycarbonyl	OMe	
875	4-amidinophenyl carbonylamino	n-butyloxycarbonyl	OH	
876	4-amidinophenyl carbonylamino	cyclopropylethoxy carbonyl	OMe	
877	4-amidinophenyl carbonylamino	cyclopropylethoxy carbonyl	OH	
878	4-amidinophenyl carbonylamino	4-methylphenylsulfonyl	OMe	
879	4-amidinophenyl carbonylamino	4-methylphenylsulfonyl	OH	
880	4-amidinophenyl carbonylamino	3-methylphenylsulfonyl	OMe	
881	4-amidinophenyl carbonylamino	3-methylphenylsulfonyl	OH	
882	4-amidinophenyl carbonylamino	n-butylsulfonyl	OMe	
883	4-amidinophenyl carbonylamino	n-butylsulfonyl	OH	
884	N-(4-amidinophenyl) amino	benzyloxycarbonyl	OMe	
885	N-(4-amidinophenyl) amino	benzyloxycarbonyl	OH	
886	N-(4-amidinophenyl) amino	n-butyloxycarbonyl	OMe	
887	N-(4-amidinophenyl) amino	n-butyloxycarbonyl	OH	

Example Number	R ¹ -V	R ¹⁶	Y	MS (M+H) ⁺
888	N-(4-amidinophenyl) amino	cyclopropylethoxy carbonyl		OMe
889	N-(4-amidinophenyl) amino	cyclopropylethoxy carbonyl		OH
890	N-(4-amidinophenyl) amino	4-methylphenylsulfonyl	OMe	
891	N-(4-amidinophenyl) amino	4-methylphenylsulfonyl	OH	
892	N-(4-amidinophenyl) amino	3-methylphenylsulfonyl	OMe	
893	N-(4-amidinophenyl) amino	3-methylphenylsulfonyl	OH	
894	N-(4-amidinophenyl) amino	n-butyloxysulfonyl		OMe
895	N-(4-amidinophenyl) amino	n-butyloxysulfonyl		OH
896	N-(4-amidinophenyl)-N- methylamino	benzyloxycarbonyl		OMe
897	N-(4-amidinophenyl)-N- methylamino	benzyloxycarbonyl		OH
898	N-(4-amidinophenyl)-N- methylamino	n-butyloxycarbonyl		OMe
899	N-(4-amidinophenyl)-N- methylamino	n-butyloxycarbonyl		OH
900	N-(4-amidinophenyl)-N- methylamino	cyclopropylethoxy carbonyl		OMe
901	N-(4-amidinophenyl)-N- methylamino	cyclopropylethoxy carbonyl		OH
902	N-(4-amidinophenyl)-N- methylamino	4-methylphenylsulfonyl	OMe	
903	N-(4-amidinophenyl)-N- methylamino	4-methylphenylsulfonyl	OH	

-234-

Example Number	R ¹ -V	R ¹⁶	Y	MS	(M+H) ⁺
904	N-(4-amidinophenyl)-N-methylamino	3-methylphenylsulfonyl	OMe		
905	N-(4-amidinophenyl)-N-methylamino	3-methylphenylsulfonyl	OH		
906	N-(4-amidinophenyl)-N-methylamino	n-butylsulfonyl	OMe		
907	N-(4-amidinophenyl)-N-methylamino	n-butylsulfonyl	OH		
908	4-amidinobenzoyl	benzyloxycarbonyl	OMe		
909	4-amidinobenzoyl	benzyloxycarbonyl	OH		
910	4-amidinobenzoyl	n-butyloxycarbonyl	OMe		
911	4-amidinobenzoyl	n-butyloxycarbonyl	OH		
912	4-amidinobenzoyl	cyclopropylethoxy carbonyl	OMe		
913	4-amidinobenzoyl	cyclopropylethoxy carbonyl	OH		
914	4-amidinobenzoyl	4-methylphenylsulfonyl	OMe		
915	4-amidinobenzoyl	4-methylphenylsulfonyl	OH		
916	4-amidinobenzoyl	3-methylphenylsulfonyl	OMe		
917	4-amidinobenzoyl	3-methylphenylsulfonyl	OH		
918	4-amidinobenzoyl	n-butylsulfonyl	OMe		
919	4-amidinobenzoyl	n-butylsulfonyl	OH		
920	4-amidinophenyl methylcarbonyl	benzyloxycarbonyl	OMe		
921	4-amidinophenyl methylcarbonyl	benzyloxycarbonyl	OH		
922	4-amidinophenyl methylcarbonyl	n-butyloxycarbonyl	OMe		
923	4-amidinophenyl methylcarbonyl	n-butyloxycarbonyl	OH		
924	4-amidinophenyl methylcarbonyl	cyclopropylethoxy carbonyl	OMe		

-235-

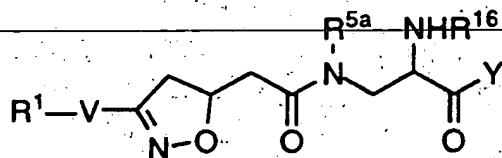
Example Number	R ¹ -V	R ¹⁶	Y	MS (M+H) ⁺
925	4-amidinophenyl methylcarbonyl	cyclopropylethoxy carbonyl	OH	
926	4-amidinophenyl methylcarbonyl	4-methylphenylsulfonyl	OMe	
927	4-amidinophenyl methylcarbonyl	4-methylphenylsulfonyl	OH	
928	4-amidinophenyl methylcarbonyl	3-methylphenylsulfonyl	OMe	
929	4-amidinophenyl methylcarbonyl	3-methylphenylsulfonyl	OH	
930	4-amidinophenyl methylcarbonyl	n-butylsulfonyl	OMe	
931	4-amidinophenyl methylcarbonyl	n-butylsulfonyl	OH	
932	4-amidinophenyl- carbonylmethyl	benzyloxycarbonyl	OMe	
933	4-amidinophenyl- carbonylmethyl	benzyloxycarbonyl	OH	
934	4-amidinophenyl- carbonylmethyl	n-butyloxycarbonyl	OMe	
935	4-amidinophenyl- carbonylmethyl	n-butyloxycarbonyl	OH	
936	4-amidinophenyl- carbonylmethyl	cyclopropylethoxy carbonyl	OMe	
937	4-amidinophenyl- carbonylmethyl	cyclopropylethoxy carbonyl	OH	
938	4-amidinophenyl- carbonylmethyl	4-methylphenylsulfonyl	OMe	
939	4-amidinophenyl- carbonylmethyl	4-methylphenylsulfonyl	OH	
940	4-amidinophenyl- carbonylmethyl	3-methylphenylsulfonyl	OMe	

-236-

Example Number	R ¹ -V	R ¹⁶	Y	MS (M+H) ⁺
941	4-amidinophenyl- carbonylmethyl	3-methylphenylsulfonyl	OH	
942	4-amidinophenyl- carbonylmethyl	n-butylsulfonyl	OMe	
943	4-amidinophenyl- carbonylmethyl	n-butylsulfonyl	OH	

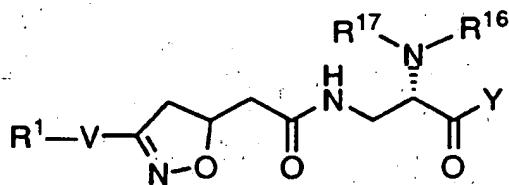
-237-

Table 2B



Example Number	R ¹ -V	R ^{5a}	R ¹⁶	Y	MS (M+H) ⁺
651	4-amidinophenyl	methyl	benzyloxycarbonyl	OMe	496
652	4-amidinophenyl	methyl	n-butyloxycarbonyl	OMe	
653	4-amidinophenyl	methyl	3-methylphenylsulfonyl	OMe	
654	4-amidinophenyl	methyl	benzyloxycarbonyl	OH	
655	4-amidinophenyl	methyl	n-butyloxycarbonyl	OH	
656	4-amidinophenyl	methyl	3-methylphenylsulfonyl	OH	
657	4-amidinophenyl	methyl	4-methylphenylsulfonyl	OH	
658	4-amidinophenyl	methyl	4-methylphenylsulfonyl	OMe	
659	4-amidinophenyl	methyl	n-butylsulfonyl	OH	
660	4-amidinophenyl	methyl	n-butylsulfonyl	OMe	

Table 2C



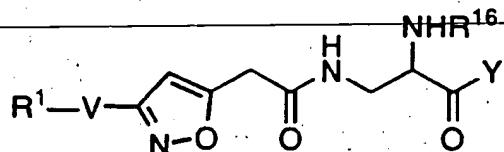
Example Number	R ¹ -V	R ¹⁶	R ¹⁷	Y	MS (M+H) ⁺
661	4-amidinophenyl	benzyloxycarbonyl	methyl	OMe	
662	4-amidinophenyl	benzyloxycarbonyl	methyl	OH	
663	4-amidinophenyl	n-butyloxycarbonyl	methyl	OMe	
664	4-amidinophenyl	n-butyloxycarbonyl	methyl	OH	

-238-

665	4-amidinophenyl	3-methylphenylsulfonyl	methyl	OMe
666	4-amidinophenyl	3-methylphenylsulfonyl	methyl	OH
667	4-amidinophenyl	4-methylphenylsulfonyl	methyl	OMe
668	4-amidinophenyl	4-methylphenylsulfonyl	methyl	OH
669	4-amidinophenyl	n-butylsulfonyl	methyl	OMe
670	4-amidinophenyl	n-butylsulfonyl	methyl	OH

-239-

Table 2D



Example Number	R ¹ -V	R ¹⁶	Y	MS (M+H) ⁺
701	4-amidinophenyl	benzyloxycarbonyl	OH	
702	4-amidinophenyl	t-butylloxycarbonyl	OH	
703	4-amidinophenyl	n-butyloxycarbonyl	OH	
704	4-amidinophenyl	ethyloxycarbonyl	OH	
705	4-amidinophenyl	methyloxycarbonyl	OH	
706	4-amidinophenyl	phenylethylcarbonyl	OH	
707	4-amidinophenyl	2,2-dimethyl- propylcarbonyl	OH	
708	4-amidinophenyl	n-pentylcarbonyl	OH	
709	4-amidinophenyl	n-butylcarbonyl	OH	
710	4-amidinophenyl	propionyl	OH	
711	4-amidinophenyl	acetyl	OH	
712	4-amidinophenyl	methylsulfonyl	OH	
713	4-amidinophenyl	ethylsulfonyl	OH	
714	4-amidinophenyl	n-butylsulfonyl	OH	
715	4-amidinophenyl	phenylsulfonyl	OH	
716	4-amidinophenyl	4-methylphenyl- sulfonyl	OH	
717	4-amidinophenyl	benzylsulfonyl	OH	
718	4-amidinophenyl	2-pyridylcarbonyl	OH	
719	4-amidinophenyl	3-pyridylcarbonyl	OH	
720	4-amidinophenyl	4-pyridylcarbonyl	OH	
721	4-amidinophenyl	2-pyridylmethyl- carbonyl	OH	
722	4-amidinophenyl	3-pyridylmethyl- carbonyl	OH	

-240-

Example Number	R ¹ -V	R ¹⁶	Y	MS (M+H) ⁺
723	4-amidinophenyl	4-pyridylmethyl- carbonyl	OH	
724	4-amidinophenyl	2-pyridylmethoxy- carbonyl	OH	
725	4-amidinophenyl	3-pyridylmethoxy- carbonyl	OH	
726	4-amidinophenyl	4-pyridylmethoxy- carbonyl	OH	
727	4-amidinophenyl	benzyloxycarbonyl	OMe	480
728	4-amidinophenyl	t-butyloxycarbonyl	OMe	
729	4-amidinophenyl	n-butyloxycarbonyl	OMe	446
730	4-amidinophenyl	ethyloxycarbonyl	OMe	
731	4-amidinophenyl	methyloxycarbonyl	OMe	
732	4-amidinophenyl	phenylethylcarbonyl	OMe	
733	4-amidinophenyl	2,2-dimethyl- propylcarbonyl	OMe	
734	4-amidinophenyl	n-pentylcarbonyl	OMe	
735	4-amidinophenyl	n-butyloxycarbonyl	OMe	
736	4-amidinophenyl	propionyl	OMe	
737	4-amidinophenyl	acetyl	OMe	
738	4-amidinophenyl	methylsulfonyl	OMe	
739	4-amidinophenyl	ethylsulfonyl	OMe	
740	4-amidinophenyl	n-butylsulfonyl	OMe	
741	4-amidinophenyl	phenylsulfonyl	OMe	
742	4-amidinophenyl	4-methylphenyl- sulfonyl	OMe	
743	4-amidinophenyl	benzylsulfonyl	OMe	
744	4-amidinophenyl	2-pyridylcarbonyl	OMe	
745	4-amidinophenyl	3-pyridylcarbonyl	OMe	
746	4-amidinophenyl	4-pyridylcarbonyl	OMe	

-241-

Example Number	R ¹ -V	R ¹⁶	Y	MS. (M+H) ⁺
747	4-amidinophenyl	2-pyridylmethyl- carbonyl	OMe	
748	4-amidinophenyl	3-pyridylmethyl- carbonyl	OMe	
749	4-amidinophenyl	4-pyridylmethyl- carbonyl	OMe	
750	4-amidinophenyl	2-pyridylmethoxy- carbonyl	OMe	
751	4-amidinophenyl	3-pyridylmethoxy- carbonyl	OMe	
752	4-amidinophenyl	4-pyridylmethoxy- carbonyl	OMe	
753	4-piperidinylethyl	benzylcarbonyl	OMe	
754	4-(BOCamidino)phenyl	benzyloxycarbonyl	OMe	
755	4-(BOCamidino)phenyl	n-butyloxycarbonyl	OMe	
756	4-amidinophenyl	1-naphthylsulfonyl	OMe	
757	4-amidinophenyl	2-naphthylsulfonyl	OMe	
758	4-piperidinylethyl	n-butyloxycarbonyl	OMe	440
759	4-amidinophenyl	2-thienylsulfonyl	OMe	
760	4-amidinophenyl	3-methylphenyl- sulfonyl	OMe	
761	4-amidinophenyl	4-fluorophenyl- sulfonyl	OMe	
762	4-amidinophenyl	4-methoxyphenyl- sulfonyl	OMe	
763	4-amidinophenyl	n-propylsulfonyl	OMe	
764	4-amidinophenyl	2-phenylethyl- sulfonyl	OMe	
765	4-amidinophenyl	4-isopropylphenyl- sulfonyl	OMe	

-242-

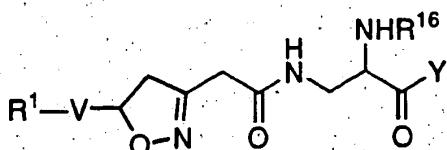
Example Number	R ¹ -V	R ¹⁶	Y	MS (M+H) ⁺
766	4-amidinophenyl	3-phenylpropyl- sulfonyl	OMe	
767	4-amidinophenyl	3-pyridylsulfonyl	OMe	
768	4-amidinophenyl	2-pyridylsulfonyl	OMe	
769	4-amidinophenyl	n-butylaminosulfonyl	OMe	
770	4-amidinophenyl	i-butylaminosulfonyl	OMe	
771	4-amidinophenyl	t-butylaminosulfonyl	OMe	
772	4-amidinophenyl	i-propylamino- sulfonyl	OMe	
773	4-amidinophenyl	cyclohexylamino- sulfonyl	OMe	
774	4-amidinophenyl	phenylaminosulfonyl	OMe	
775	4-amidinophenyl	benzylaminosulfonyl	OMe	
776	4-amidinophenyl	dimethylamino- sulfonyl	OMe	
777	2-fluoro-4-amidino- phenyl	3-methylphenyl- sulfonyl	OMe	
778	5-amidino-2-pyridyl	n-butyloxycarbonyl	OMe	
779	5-amidino-2-pyridyl	3-methylphenyl- sulfonyl	OMe	
780	6-amidino-3-pyridyl	n-butyloxycarbonyl	OMe	
781	6-amidino-3-pyridyl	3-methylphenyl- sulfonyl	OMe	
782	4-amidinophenyl	phenylaminocarbonyl	OMe	
783	4-amidinophenyl	benzylaminocarbonyl	OMe	
784	4-amidinophenyl	n-butylaminocarbonyl	OMe	
785	4-amidinophenyl	n-hexyloxycarbonyl	OMe	
786	4-amidinophenyl	n-hexyloxycarbonyl	OH	
787	4-amidinophenyl	isobutyloxycarbonyl	OMe	
788	4-amidinophenyl	isobutyloxycarbonyl	OH	
789	4-amidinophenyl	2-cyclopropylethoxy- carbonyl	OMe	

-243-

Example Number	R ¹ -V	R ¹⁶	Y	MS (M+H) ⁺
790	4-amidinophenyl	2-cyclopropylethoxy- carbonyl	OH	
791	4-amidinophenyl	2-cyclopentylethoxy- carbonyl	OMe	
792	4-amidinophenyl	2-cyclopentylethoxy- carbonyl	OH	
793	4-amidinophenyl	n-propylsulfonyl	OMe	
794	4-amidinophenyl	2-methylphenyl- sulfonyl	OMe	
795	4-amidinophenyl	2-benzothienyl- sulfonyl	OMe	
796	4-amidinophenyl	2-benzothienyl- sulfonyl	OMe	
797	4-amidinophenyl	2,2,5,7,8-pentamethyl 3,4-dihydro-2Hbenzo- pyran-6-ylsulfonyl	OH	
798	4-amidinophenyl	3-methylphenylsulfonyl	OH	486

-244-

Table 2E



Example Number	R ¹ -V	R ¹⁶	Y	MS (M+H) ⁺
801	4-amidinophenyl	benzyloxycarbonyl	OH	
802	4-amidinophenyl	t-butyloxycarbonyl	OH	
803	4-amidinophenyl	n-butyloxycarbonyl	OH	
804	4-amidinophenyl	ethyloxycarbonyl	OH	
805	4-amidinophenyl	methyloxycarbonyl	OH	
806	4-amidinophenyl	phenylethylcarbonyl	OH	
807	4-amidinophenyl	2,2-dimethyl- propylcarbonyl	OH	
808	4-amidinophenyl	n-pentylcarbonyl	OH	
809	4-amidinophenyl	n-butyloxycarbonyl	OH	
810	4-amidinophenyl	propionyl	OH	
811	4-amidinophenyl	acetyl	OH	
812	4-amidinophenyl	methylsulfonyl	OH	
813	4-amidinophenyl	ethylsulfonyl	OH	
814	4-amidinophenyl	n-butylsulfonyl	OH	
815	4-amidinophenyl	phenylsulfonyl	OH	
816	4-amidinophenyl	4-methylphenyl- sulfonyl	OH	
817	4-amidinophenyl	benzylsulfonyl	OH	
818	4-amidinophenyl	2-pyridylcarbonyl	OH	
819	4-amidinophenyl	3-pyridylcarbonyl	OH	
820	4-amidinophenyl	4-pyridylcarbonyl	OH	
821	4-amidinophenyl	2-pyridylmethyl- carbonyl	OH	
822	4-amidinophenyl	3-pyridylmethyl- carbonyl	OH	

Example Number	R ¹ -Y	R ¹⁶	Y	MS (M+H) ⁺
823	4-amidinophenyl	4-pyridylmethyl-	OH	
		carbonyl		
824	4-amidinophenyl	2-pyridylmethoxy-	OH	
		carbonyl		
825	4-amidinophenyl	3-pyridylmethoxy-	OH	
		carbonyl		
826	4-amidinophenyl	4-pyridylmethoxy-	OH	
		carbonyl		
827	4-amidinophenyl	benzyloxycarbonyl	OMe	
828	4-amidinophenyl	t-butyloxycarbonyl	OMe	
829	4-amidinophenyl	n-butyloxycarbonyl	OMe	448
830	4-amidinophenyl	ethyloxycarbonyl	OMe	
831	4-amidinophenyl	methyloxycarbonyl	OMe	
832	4-amidinophenyl	phenylethylcarbonyl	OMe	
833	4-amidinophenyl	2,2-dimethyl-	OMe	
		propylcarbonyl		
834	4-amidinophenyl	n-pentylcarbonyl	OMe	
835	4-amidinophenyl	n-butylcarbonyl	OMe	
836	4-amidinophenyl	propionyl	OMe	
837	4-amidinophenyl	acetyl	OMe	
838	4-amidinophenyl	methylsulfonyl	OMe	
839	4-amidinophenyl	ethylsulfonyl	OMe	
840	4-amidinophenyl	n-butylsulfonyl	OMe	
841	4-amidinophenyl	phenylsulfonyl	OMe	
842	4-amidinophenyl	4-methylphenyl-	OMe	
		sulfonyl		
843	4-amidinophenyl	benzylsulfonyl	OMe	
844	4-amidinophenyl	2-pyridylcarbonyl	OMe	
845	4-amidinophenyl	3-pyridylcarbonyl	OMe	
846	4-amidinophenyl	4-pyridylcarbonyl	OMe	

-246-

Example Number	R ¹ -V	R ¹⁶	Y	MS (M+H) ⁺
847	4-amidinophenyl	2-pyridylmethyl- carbonyl	OMe	
848	4-amidinophenyl	3-pyridylmethyl- carbonyl	OMe	
849	4-amidinophenyl	4-pyridylmethyl- carbonyl	OMe	
850	4-amidinophenyl	2-pyridylmethoxy- carbonyl	OMe	
851	4-amidinophenyl	3-pyridylmethoxy- carbonyl	OMe	
852	4-amidinophenyl	4-pyridylmethoxy- carbonyl	OMe	
853	4-piperidinylethyl	benzylcarbonyl	OMe	
854	4-(BOCamidino)phenyl	benzyloxycarbonyl	OMe	
855	4-(BOCamidino)phenyl	n-butyloxycarbonyl	OMe	
856	4-amidinophenyl	1-naphthylsulfonyl	OMe	
857	4-amidinophenyl	2-naphthylsulfonyl	OMe	
858	4-piperidinylethyl	n-butyloxycarbonyl	OMe	
859	4-amidinophenyl	2-thienylsulfonyl	OMe	
860	4-amidinophenyl	3-methylphenyl- sulfonyl	OMe	
861	4-amidinophenyl	4-fluorophenyl- sulfonyl	OMe	
862	4-amidinophenyl	4-methoxyphenyl- sulfonyl	OMe	
863	4-amidinophenyl	n-propylsulfonyl	OMe	
864	4-amidinophenyl	2-phenylethyl- sulfonyl	OMe	
865	4-amidinophenyl	4-isopropylphenyl- sulfonyl	OMe	

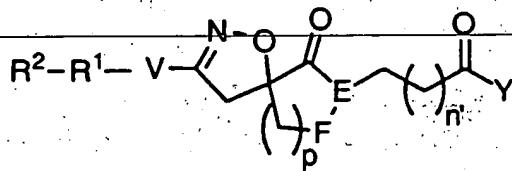
-247-

Example Number	R ¹ -v	R ¹⁶	Y	MS (M+H) ⁺
866	4-amidinophenyl	3-phenylpropyl- sulfonyl	OMe	
867	4-amidinophenyl	3-pyridylsulfonyl	OMe	
868	4-amidinophenyl	2-pyridylsulfonyl	OMe	
869	4-amidinophenyl	n-butylaminosulfonyl	OMe	
870	4-amidinophenyl	i-butylaminosulfonyl	OMe	
871	4-amidinophenyl	t-butylaminosulfonyl	OMe	
872	4-amidinophenyl	i-propylamino- sulfonyl	OMe	
873	4-amidinophenyl	cyclohexylamino- sulfonyl	OMe	
874	4-amidinophenyl	phenylaminosulfonyl	OMe	
875	4-amidinophenyl	benzylaminosulfonyl	OMe	
876	4-amidinophenyl	dimethylamino- sulfonyl	OMe	
877	2-fluoro-4-amidino- phenyl	3-methylphenyl- sulfonyl	OMe	
878	5-amidino-2-pyridyl	n-butyloxycarbonyl	OMe	
879	5-amidino-2-pyridyl	3-methylphenyl- sulfonyl	OMe	
880	6-amidino-3-pyridyl	n-butyloxycarbonyl	OMe	
881	6-amidino-3-pyridyl	3-methylphenyl- sulfonyl	OMe	
882	4-amidinophenyl	phenylaminocarbonyl	OMe	
883	4-amidinophenyl	benzylaminocarbonyl	OMe	
884	4-amidinophenyl	n-butylaminocarbonyl	OMe	
885	4-amidinophenyl	n-hexyloxycarbonyl	OMe	
886	4-amidinophenyl	n-hexyloxycarbonyl	OH	
887	4-amidinophenyl	isobutyloxycarbonyl	OMe	
888	4-amidinophenyl	isobutyloxycarbonyl	OH	
889	4-amidinophenyl	2-cyclopropylethoxy- carbonyl	OMe	

-248-

Example Number	R ¹ -V	R ¹⁶	Y	MS (M+H) ⁺
890	4-amidinophenyl	2-cyclopropylethoxy- carbonyl	OH	
891	4-amidinophenyl	2-cyclopentylethoxy- carbonyl	OMe	
892	4-amidinophenyl	2-cyclopentylethoxy- carbonyl	OH	
893	4-amidinophenyl	n-propylsulfonyl	OMe	
894	4-amidinophenyl	2-methylphenyl- sulfonyl	OMe	
895	4-amidinophenyl	2-benzothienyl- sulfonyl	OMe	
896	4-amidinophenyl	2-benzothienyl- sulfonyl	OMe	
897	4-amidinophenyl	2,2,5,7,8-pentamethyl 3,4-dihydro-2Hbenzo- pyran-6-ylsulfonyl	OH	

Table 3



(VII)

Ex. No.	R ²	R ¹ -V	-F-E<	p	n'	Y
171	H		-C(=O)-N<	1	1	OH
172	H		-C(=O)-N<	1	2	OH
173	H		-C(H ₂)-N<	1	1	OH
174	H		-C(H ₂)-N<	1	2	OH
175	H		-C(H)=C<	1	1	OH
176	H		-C(H)=C<	1	2	OH
177	H		-C(=O)-N<	2	1	OH
178	H		-C(=O)-N<	2	2	OH
179	H		-C(H ₂)-N<	2	1	OH
180	H		-C(H ₂)-N<	2	2	OH
181	H		-C(H)=C<	2	1	OH
182	H		-C(H)=C<	2	2	OH
183	H		-C(=O)-N<	3	1	OH
184	H		-C(=O)-N<	3	2	OH
185	H		-C(H ₂)-N<	3	1	OH
186	H		-C(H ₂)-N<	3	2	OH
187	H		-C(H)=C<	3	1	OH
188	H		-C(H)=C<	3	2	OH

Ex. No.	R ²	R ¹ -V	-F-E<	p	n'	Y
189	H		-C(=O)-N< 1	1		OH
190	H		-C(=O)-N< 1	2		OH
191	H		-C(H ₂)-N< 1	1		OH
192	H		-C(H ₂)-N< 1	2		OH
193	H		-C(H)=C< 1	1		OH
194	H		-C(H)=C< 1	2		OH
195	H		-C(=O)-N< 2	1		OH
196	H		-C(=O)-N< 2	2		OH
197	H		-C(H ₂)-N< 2	1		OH
198	H		-C(H ₂)-N< 2	2		OH
199	H		-C(H)=C< 2	1		OH
200	H		-C(H)=C< 2	2		OH
201	H		-C(=O)-N< 3	1		OH
202	H		-C(=O)-N< 3	2		OH
203	H		-C(H ₂)-N< 3	1		OH
204	H		-C(H ₂)-N< 3	2		OH
205	H		-C(H)=C< 3	1		OH
206	H		-C(H)=C< 3	2		OH
207	Boc		-C(=O)-N< 1	1		OH
208	Cbz		-C(=O)-N< 1	1		OH
209	H		-C(=O)-N< 1	1		
210	H		-C(=O)-N< 1	1		
211	H		-C(=O)-N< 1	1		
212	H		-C(=O)-N< 1	1		
213	H		-C(=O)-N< 1	1		
214	H		-C(=O)-N< 1	1		OEt

Ex. No.	R ²	R ¹ -V	-F-E<	p	n'	Y
215	H		-C(=O)-N<	1	2	OEt
216	H		-C(H ₂)-N<	1	1	OEt
217	H		-C(H ₂)-N<	1	2	OEt
218	H		-C(H)=C<	1	1	OEt
219	H		-C(H)=C<	1	2	OEt
220	H		-C(=O)-N<	2	1	OEt
221	H		-C(=O)-N<	2	2	OEt
222	H		-C(H ₂)-N<	2	1	OEt
223	H		-C(H ₂)-N<	2	2	OEt
224	H		-C(H)=C<	2	1	OEt
225	H		-C(H)=C<	2	2	OEt
226	H		-C(=O)-N<	3	1	OEt
227	H		-C(=O)-N<	3	2	OEt
228	H		-C(H ₂)-N<	3	1	OEt
229	H		-C(H ₂)-N<	3	2	OEt
230	H		-C(H)=C<	3	1	OEt
231	H		-C(H)=C<	3	2	OEt
232	H		-C(=O)-N<	1	1	OEt
233	H		-C(=O)-N<	1	2	OEt
234	H		-C(H ₂)-N<	1	1	OEt
235	H		-C(H ₂)-N<	1	2	OEt
236	H		-C(H)=C<	1	1	OEt
237	H		-C(H)=C<	1	2	OEt
238	H		-C(=O)-N<	2	1	OEt
239	H		-C(=O)-N<	2	2	OEt
240	H		-C(H ₂)-N<	2	1	OEt

-252-

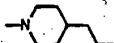
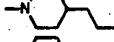
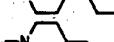
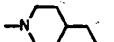
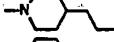
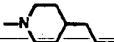
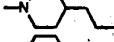
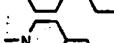
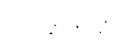
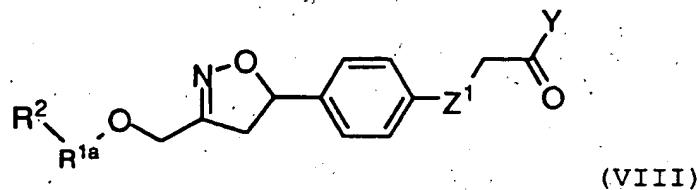
Ex. No.	R ²	R ¹ -V	-F-E<	p	n'	Y
241	H		-C(H ₂)-N<	2		OEt
242	H		-C(H)=C<	2	1	OEt
243	H		-C(H)=C<	2	2	OEt
244	H		-C(=O)-N<	3	1	OEt
245	H		-C(=O)-N<	3	2	OEt
246	H		-C(H ₂)-N<	3	1	OEt
247	H		-C(H ₂)-N<	3	2	OEt
248	H		-C(H)=C<	3	1	OEt
249	H		-C(H)=C<	3	2	OEt
250	Boc		-C(=O)-N<	1	1	OEt
251	Cbz		-C(=O)-N<	1	1	OEt
373	H		-C(=O)-N<	1	2	OH

Table 4



Example Number	R ²	R ^{1a}	Z ¹	Y
252	H		CH ₂	OH
253	H		CH ₂	OH
254	H		CH ₂	OH
255	H		O	OH
256	H		O	OH
257	H		O	OH
258	Boc		CH ₂	OH
259	Cbz		CH ₂	OH
260	H		CH ₂	
261	H		CH ₂	
262	H		CH ₂	
263	H		CH ₂	
264	H		CH ₂	
265	H		CH ₂	OEt
266	H		CH ₂	OEt
267	H		CH ₂	OEt
268	H		CH ₂	OEt
269	H		CH ₂	OEt
270	H		O	OEt
271	H		O	OEt
272	H		O	OEt

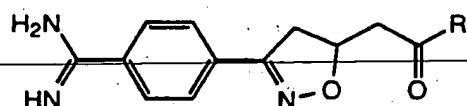
-254-

Example Number	R ²	R ^{1a}	z ¹	Y
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273	Boc		CH ₂	OEt
274	Cbz		CH ₂	OEt

-255-

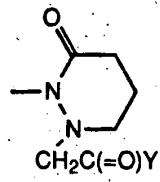
Table 5



Example Number	R	Y	MS (ESI) (M+H) ⁺
375		OH	373
376		OH	
377		OH	387
378		OH	
379		OH	
380		OH	
381		OH	
382		OH	

-256-

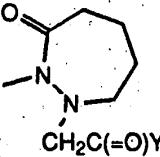
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OH

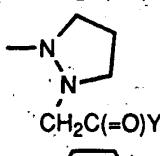
415

384



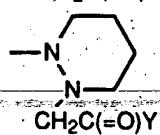
OH

385



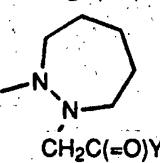
OH

386



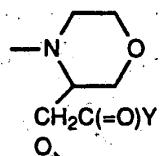
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387



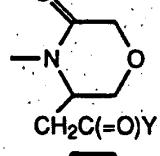
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388



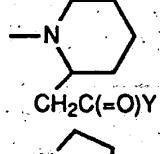
OH

389



OH

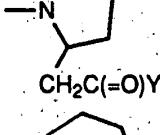
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OMe

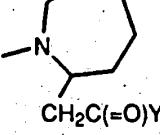
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395



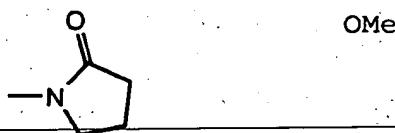
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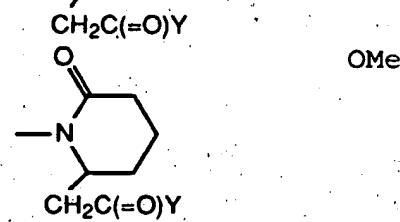


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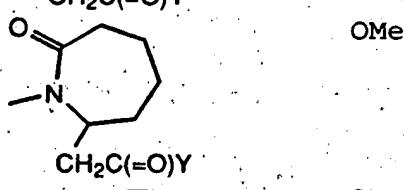
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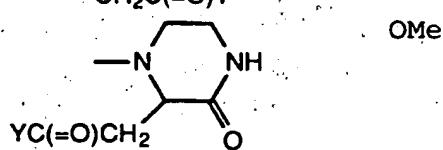
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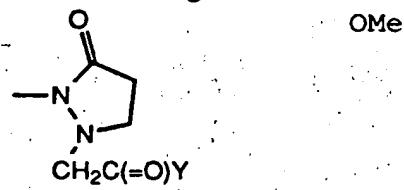
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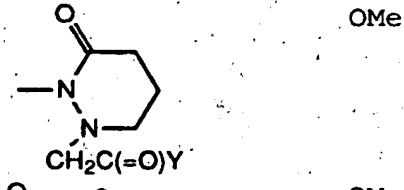
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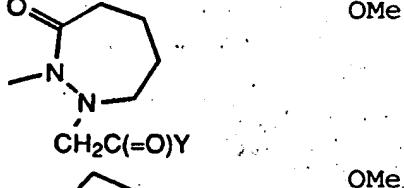
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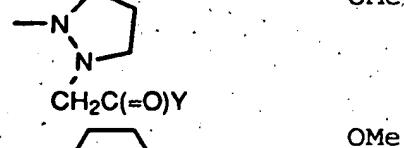
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403



404

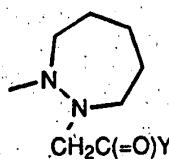


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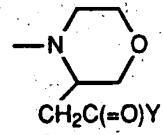


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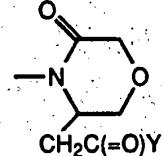
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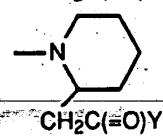
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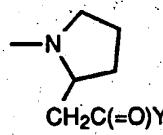
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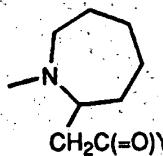
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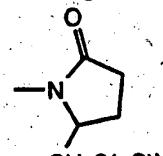
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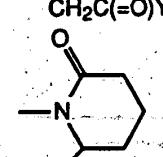
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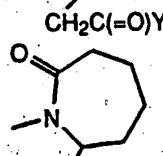
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417



418



OMe

OMe

OMe

OEt

401

OEt

415

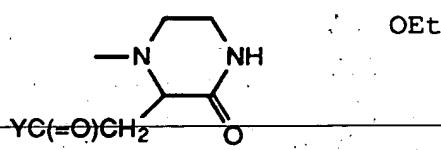
OEt

OEt

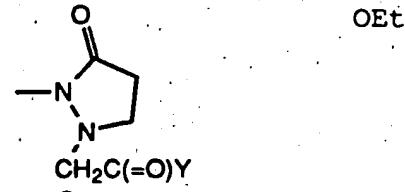
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-259-

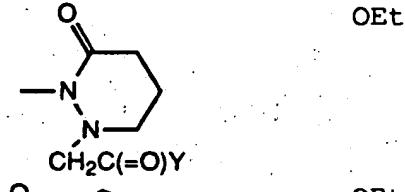
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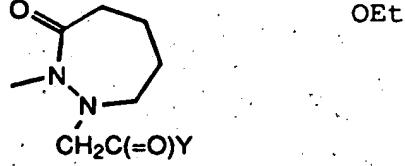
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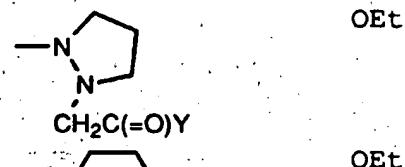
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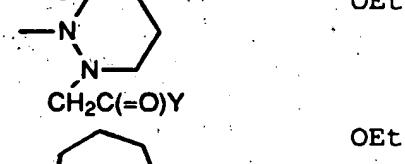
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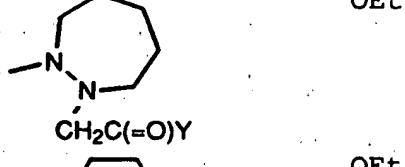
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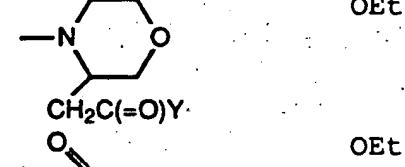
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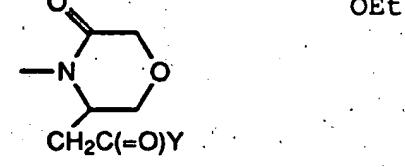
425



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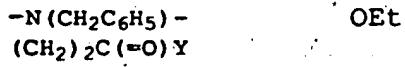
427



432

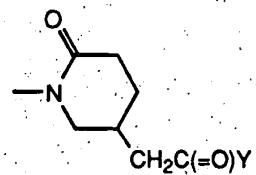


433

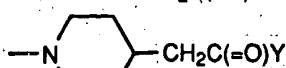


-260-

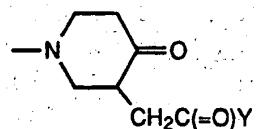
436



437



438



OEt

387

OEt

387

OMe

387

Utility

The compounds of this invention possess antiplatelet efficacy, as evidenced by their activity in standard platelet aggregation assays or platelet fibrinogen binding assays, as described below. A compound is considered to be active in these assays if it has an IC₅₀ value of less than about 1 mM. Platelet aggregation and fibrinogen binding assays which may be used to demonstrate the antiplatelet activity of the compounds of the invention are described below.

Platelet Aggregation Assay: Venous blood was obtained from the arm of a healthy human donor who was drug-free and aspirin-free for at least two weeks prior to blood collection. Blood was collected into 10 mL citrated Vacutainer tubes. The blood was centrifuged for 15 minutes at 150 x g at room temperature, and platelet-rich plasma (PRP) was removed. The remaining blood was centrifuged for 15 minutes at 1500 x g at room temperature, and platelet-poor plasma (PPP) was removed. Samples were assayed on a aggregometer (PAP-4 Platelet Aggregation Profiler), using PPP as the blank (100% transmittance). 200 μ L of PRP was added to each micro test tube, and transmittance was set to 0%. 20 μ L of various agonists (ADP, collagen, arachidonate, epinephrine, thrombin) were added to each tube, and the aggregation profiles were plotted (% transmittance versus time). The results are expressed as % inhibition of agonist-induced platelet aggregation. For the IC₅₀ evaluation, the test compounds were added at various concentrations prior to the activation of the platelets. Ester prodrugs were preincubated (10⁻³ M F.C.) with 100 IU/ml Porcine liver esterase (Sigma Chemical Co., St. Louis, MO, #E-3128) for 2 hours at 37 °C. Aliquots

are then diluted in 0.1 M Tris, pH 7.4, to the desired concentrations. Aliquots of 20 μ l of the esterase pretreated prodrugs are added to 200 μ l of human platelet rich plasma. Samples were placed in platelet profiler (aggregometer) for 8 minutes at 37 °C, followed by the addition of 100 μ M Adenosine Diphosphate, (Sigma Chemical Co., St. Louis, MO, #A-6521), to induce platelet aggregation. Platelet aggregation was allowed to proceed for 5 minutes. Percent inhibition is calculated using percent aggregation in the presence of the test compound divided by percent aggregation of control, times 100. This value is subtracted from 100, yielding percent inhibition. Calculation of IC₅₀ is performed on a Texas Instruments TI59 with an IC₅₀ program.

Purified GPIIb/IIIa-Fibrinogen Binding ELISA

The following reagents are used in the 20. GPIIb/IIIa-fibrinogen binding ELISA:

purified GPIIb/IIIa (148.8 μ g/mL);
biotinylated fibrinogen (~ 1 mg/mL or 3000 nM);
anti-biotin alkaline phosphatase conjugate (Sigma no. A7418);
25. flat-bottom, high binding, 96-well plates
(Costar Cat. no. 3590);
phosphatase substrate (Sigma 104) (40 mg capsules);
bovine serum albumin (BSA) (Sigma no. A3294);
Alkaline Phosphatase buffer - 0.1 M glycine-HCl, 1
30. mM MgCl₂.6H₂O, 1 mM ZnCl₂, pH 10.4;
Binding buffer - 20 mM Tris-HCl, 150 mM NaCl, 1 mM
CaCl₂.2H₂O, 0.02% NaN₃, pH 7.0;
Buffer A - 50 mM Tris-HCl, 100 mM NaCl, 2 mM
CaCl₂.2H₂O, 0.02% NaN₃, pH 7.4;
35. Buffer A + 3.5% BSA (Blocking buffer);

Buffer A + 0.1% BSA (Dilution buffer);
2N NaOH.

The following method steps are used in the

5 GPIIb/IIIa-fibrinogen binding ELISA:

Coat plates with GPIIb/IIIa in Binding buffer (125 ng/100 μ L/well) overnight at 4 °C (Leave first column uncoated for non-specific binding). Cover and freeze plates at -70 °C until used. Thaw plate 1 hour at room

10 temperature or overnight at 4 °C. Discard coating solution and wash once with 200 μ L Binding buffer per well. Block plate 2 hours at room temperature on shaker with 200 μ L Buffer A + 3.5% BSA (Blocking buffer) per well. Discard Blocking buffer and wash once with 200 μ L

15 Buffer A + 0.1% BSA (Dilution buffer) per well. Pipet 11 μ L of test compound (10X the concentration to be tested in Dilution buffer) into duplicate wells. Pipet 11 μ L Dilution buffer into non-specific and total binding wells. Add 100 μ L Biotinylated fibrinogen

20 (1/133 in Dilution buffer, final concentration = 20 nM) to each well. Incubate plates for 3 hours at room temperature on a plate shaker. Discard assay solution and wash twice with 300 μ L Binding buffer per well. Add 100 μ L Anti-biotin alkaline phosphatase conjugate

25 (1/1500 in Dilution buffer) to each well. Incubate plates for 1 hour at room temperature on plate shaker. Discard conjugate and wash twice with 300 μ L Binding buffer per well. Add 100 μ L Phosphatase substrate (1.5 mg/ml in Alkaline phosphatase buffer) to each well.

30 Incubate plate at room temperature on shaker until color develops. Stop color development by adding 25 μ L 2N NaOH per well. Read plate at 405 nm. Blank against non-specific binding (NSB) well. % Inhibition is calculated as

35 $100 - (\text{Test Compound Abs}/\text{Total Abs}) \times 100$.

Platelet-Fibrinogen Binding Assay: Binding of ^{125}I -fibrinogen to platelets was performed as described by Bennett et al. (1983) Proc. Natl. Acad. Sci. USA 80: 2417-2422, with some modifications as described below.

5 Human PRP (h-PRP) was applied to a Sepharose column for the purification of platelet fractions. Aliquots of platelets (5×10^8 cells) along with 1 mM calcium chloride were added to removable 96 well plates prior to the activation of the human gel purified platelets (h-GPP). Activation of the human gel purified platelets was achieved using ADP, collagen, arachidonate, epinephrine, and/or thrombin in the presence of the ligand, ^{125}I -fibrinogen. The ^{125}I -fibrinogen bound to the activated platelets was separated from the free form by centrifugation and then counted on a gamma counter. For an IC_{50} evaluation, the test compounds were added at various concentrations prior to the activation of the platelets.

20 The compounds of Formula I of the present invention may also possess thrombolytic efficacy, that is, they are capable of lysing (breaking up) already formed platelet-rich fibrin blood clots, and thus are useful in treating a thrombus formation, as evidenced by their 25 activity in the tests described below. Preferred compounds of the present invention for use in thrombolysis include those compounds having an IC_{50} value (that is, the molar concentration of the compound capable of achieving 50% clot lysis) of less than about 30 1 μM , more preferably an IC_{50} value of less than about 0.1 μM .

Thrombolytic Assay: Venous blood was obtained from the arm of a healthy human donor who was drug-free and aspirin free for at least two weeks prior to blood

collection, and placed into 10 ml citrated Vacutainer tubes. The blood was centrifuged for 15 minutes at 1500 x g at room temperature, and platelet rich plasma (PRP) was removed. To the PRP was then added 1 x 10⁻³ M of the agonist ADP, epinephrine, collagen, arachidonate, serotonin or thrombin, or a mixture thereof, and the PRP incubated for 30 minutes. The PRP was centrifuged for 12 minutes at 2500 x g at room temperature. The supernatant was then poured off, and the platelets remaining in the test tube were resuspended in platelet poor plasma (PPP), which served as a plasminogen source. The suspension was then assayed on a Coulter Counter (Coulter Electronics, Inc., Hialeah, FL), to determine the platelet count at the zero time point. After obtaining the zero time point, test compounds were added at various concentrations. Test samples were taken at various time points and the platelets were counted using the Coulter Counter. To determine the percent of lysis, the platelet count at a time point subsequent to the addition of the test compound was subtracted from the platelet count at the zero time point, and the resulting number divided by the platelet count at the zero time point. Multiplying this result by 100 yielded the percentage of clot lysis achieved by the test compound. For the IC₅₀ evaluation, the test compounds were added at various concentrations, and the percentage of lysis caused by the test compounds was calculated.

The compounds of Formula I of the present invention are also useful for administration in combination with anti-coagulant agents such as warfarin or heparin, or antiplatelet agents such as aspirin, piroxicam or ticlopidine, or thrombin inhibitors such as boropeptides, hirudin or argatroban, or thrombolytic agents such as tissue plasminogen activator.

266

anistreplase, urokinase or streptokinase, or combinations thereof.

The compounds of Formula I of the present invention 5 may also be useful as antagonists of other integrins such as for example, the α_v/β_3 or vitronectin receptor, α_4/β_1 or α_5/β_1 and as such may also have utility in the treatment and diagnosis of osteoporosis, cancer, metastasis, diabetic retinopathy, rheumatoid arthritis, 10 inflammation, and autoimmune disorders. The compounds of Formula I of the present invention may be useful for the treatment or prevention of other diseases which involve cell adhesion processes, including, but not limited to, inflammation, bone degradation, rheumatoid 15 arthritis, asthma, allergies, adult respiratory distress syndrome, graft versus host disease, organ transplantation, septic shock, psoriasis, eczema, contact dermatitis, osteoporosis, osteoarthritis, atherosclerosis, metastasis, wound healing, diabetic 20 retinopathy, inflammatory bowel disease and other autoimmune diseases.

Table A below sets forth the antiplatelet activity 25 of representative compounds of the present invention. The indicated compounds were tested for their ability to inhibit platelet aggregation (using platelet rich plasma (PRP)). The IC₅₀ value (the concentration of antagonist which inhibits platelet aggregation by 50% relative to a 30 control lacking the antagonist) is shown. In Table 5 the IC₅₀ values are expressed as: +++ = IC₅₀ of <10 μ M; ++ = IC₅₀ of 10-50 μ M; + = IC₅₀ of 50-100 μ M (μ M = micromolar).

267

Table A

<u>Example Number</u>	<u>Platelet</u>	<u>Platelet</u>
	<u>Aggregation Assay</u> <u>IC₅₀ (without esterase)</u>	<u>Aggregation Assay</u> <u>IC₅₀ (with esterase)</u>
1	+++	
4 (isomer A)	++	
4 (isomer B)	++	
6	+++	
7	>100	
8	+	
9 (isomer A)	+++	
9 (isomer B)	+++	
33	>100	
43	+++	
89		+++
115		+++
119A (3R)		+++
119B (3S)		+++
120A (3R)		+++
120B (3S)		+++
120C (3R) ††		+++
166		+++
189	>100	
190	+	
275		+++
276		+++
278		+++
290		+++
300		+++
312		+++
314A (2S) †		+++
314B (2S) ††		+++
323		+++
324		+++

268

326	+++
327 (2S)	+++
328 (2S)	+++
338 (3S)	+
339 (3S)	+++
340 (3S)	+
341 (3S)	+++
342 (2S)	+++
344 (3R)	+++
345	+++
347 (3R) ††	+++
348 (3R)	+++
350	+++
359	+++
362	+++
365	+++
368	+++
373	++
371A	+++
371B	+++
374 (2S)	+
375*	+++
377	+++
394	+++
394Att	+++
400	+++
413*	+++
415	+++
435	+++
436	+++
437	+++
438	+++
439	+++
440	+++
441	+++

269

442	+++
443 (2S)	+++
444 (2S)	+++
445 (2S)	+++
446	+++
449A	+++
449B	+++
450	+++
451	+++
452	+++
453	+++
454	+++
455	+++
456	++
457	+++
458A	+++
458B	+++
460A	+++
460B	+++
462	+++
463	+++
464	+++
465	+++
466	+++
467	+++
468	+++
469	+++
470	+++
471	+++
472	+++
473	+++
473A (2S) †	+++
473B (2S) ††	+++
474	+++
475	+++

270

476	+++
477	+++
478	+++
479	+++
480	+++
481	+++
482	+++
483	+++
484	+++
485	+++
486	+++
487	+++
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518	+++
519	+++
520	+++
522	+++
523	+++
524	+++
525	+++
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527	+++
528	+++
529	+++
530	+++
531	+++
532	+++
533	+++
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535	+++
536	+++
537	+++
538	+++
539	+++
540	+++
541	+++
542	+++
543	+++
544	+++
545	+++
546	+++
547	+++
548	+++
549	+++
550	+++
551	+++
552	+++
553	+++

272

554	+++
555	+++
556	+++
587A (2S)††	+++
588	+++
602	+++
611	+++
612	+++
613	+++
616	+++
651	+++
727	+++
729	+++
798	+++
829	+++

* Single diastereomer, racemic

† S isomer at C5 of isoxazoline ring

†† R isomer at C5 of isoxazoline ring

5

Dosage and Formulation

The compounds of the present invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. Likewise, they may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as an anti-aggregation agent.

The compounds of this invention can be administered by any means that produces contact of the active agent with the agent's site of action, glycoprotein IIb/IIIa (GPIIb/IIIa), in the body of a mammal. They can be

administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents, such as a second antiplatelet agent 5 such as aspirin or ticlopidine which are agonist-specific. They can be administered alone, but generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

10 The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical 15 condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient, and the effect desired. An ordinarily skilled 20 physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the condition.

25 By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to 1000 mg/kg of body weight, preferably between about 0.01 to 100 mg/kg of body weight per day, and most preferably between 30 about 1.0 to 20 mg/kg/day. Intravenously, the most preferred doses will range from about 1 to about 10 mg/kg/minute during a constant rate infusion. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total 35 daily dosage may be administered in divided doses of two, three, or four times daily.

5 The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

10 In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as "carrier materials") suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

15 For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Moreover, when desired or necessary, suitable binders, 20 lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, 25 waxes, and the like. Lubricants used in these dosage

forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, 5 xanthan gum, and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be 10 formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

Compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include 15 polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may 20 be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, 25 polyacetals, polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

Dosage forms (pharmaceutical compositions) suitable 30 for administration may contain from about 1 milligram to about 100 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the 35 composition.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups, and suspensions. It can also be administered 5 parenterally, in sterile liquid dosage forms.

Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make 10 compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the

15 tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

20 In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions.

Solutions for parenteral administration preferably 25 contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents.

30 Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in 35 Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field.

Representative useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

5 A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

10 Soft Gelatin Capsules

A mixture of active ingredient in a digestable oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin 15 capsules containing 100 milligrams of the active ingredient. The capsules are washed and dried.

Tablets

20 A large number of tablets are prepared by conventional procedures so that the dosage unit was 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase 25 palatability or delay absorption.

Injectable

25 A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution is made 30 isotonic with sodium chloride and sterilized.

Suspension

An aqueous suspension is prepared for oral administration so that each 5 mL contain 100 mg of 35 finely divided active ingredient, 200 mg of sodium

carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 mL of vanillin.

The compounds of the present invention may be
5 administered in combination with a second therapeutic
agent selected from: an anti-coagulant agent such as
warfarin or heparin; an anti-platelet agent such as
aspirin, piroxicam or ticlopidine; a thrombin inhibitor
such as a boropeptide thrombin inhibitor, or hirudin; or
10 a thrombolytic agent such as plasminogen activators,
such as tissue plasminogen activator, anistreplase,
urokinase or streptokinase. The compound of Formula I
and such second therapeutic agent can be administered
separately or as a physical combination in a single
15 dosage unit, in any dosage form and by various routes of
administration, as described above.

The compound of Formula I may be formulated
together with the second therapeutic agent in a single
dosage unit (that is, combined together in one capsule,
20 tablet, powder, or liquid, etc.). When the compound of
Formula I and the second therapeutic agent are not
formulated together in a single dosage unit, the
compound of Formula I and the second therapeutic agent
(anti-coagulant agent, anti-platelet agent, thrombin
25 inhibitor, and/or thrombolytic agent) may be
administered essentially at the same time, or in any
order; for example the compound of Formula I may be
administered first, followed by administration of the
second agent (anti-coagulant agent, anti-platelet agent,
30 thrombin inhibitor, and/or thrombolytic agent). When
not administered at the same time, preferably the
administration of the compound of Formula I and the
second therapeutic agent occurs less than about one hour
apart.

A preferable route of administration of the compound of Formula I is oral. Although it is preferable that the compound of Formula I and the second therapeutic agent (anti-coagulant agent, anti-platelet agent, thrombin inhibitor, and/or thrombolytic agent) are both administered by the same route (that is, for example, both orally), if desired, they may each be administered by different routes and in different dosage forms (that is, for example, one component of the combination product may be administered orally, and another component may be administered intravenously).

The dosage of the compound of Formula I when administered alone or in combination with a second therapeutic agent may vary depending upon various factors such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration, the age, health and weight of the recipient, the nature and extent of the symptoms, the kind of concurrent treatment, the frequency of treatment, and the effect desired, as described above.

Although the proper dosage of the compound of Formula I when administered in combination with the second therapeutic agent will be readily ascertainable by a medical practitioner skilled in the art, once armed with the present disclosure, by way of general guidance, where the compounds of this invention are combined with anti-coagulant agents, for example, a daily dosage may be about 0.1 to 100 milligrams of the compound of Formula I and about 1 to 7.5 milligrams of the anti-coagulant, per kilogram of patient body weight. For a tablet dosage form, the novel compounds of this invention generally may be present in an amount of about 1 to 10 milligrams per dosage unit, and the anti-coagulant in an amount of about 1 to 5 milligrams per dosage unit.

Where the compounds of Formula I are administered in combination with a second anti-platelet agent, by way of general guidance, typically a daily dosage may be about 0.01 to 25 milligrams of the compound of Formula I and about 50 to 150 milligrams of the additional anti-platelet agent, preferably about 0.1 to 1 milligrams of the compound of Formula I and about 1 to 3 milligrams of antiplatelet agents, per kilogram of patient body weight.

Further, by way of general guidance, where the compounds of Formula I are administered in combination with thrombolytic agent, typically a daily dosage may be about 0.1 to 1 milligrams of the compound of Formula I, per kilogram of patient body weight and, in the case of the thrombolytic agents, the usual dosage of the thrombolytic agent when administered alone may be reduced by about 70-80% when administered with a compound of Formula I.

Where two or more of the foregoing second therapeutic agents are administered with the compound of Formula I, generally the amount of each component in a typical daily dosage and typical dosage form may be reduced relative to the usual dosage of the agent when administered alone, in view of the additive or synergistic effect of the therapeutic agents when administered in combination.

Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between the combined active ingredients. For this reason, when the compound of Formula I and a second therapeutic agent are combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized (that is, reduced). For example, one active ingredient may be enteric coated. By enteric coating one of the active

ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that 5 one of these components is not released in the stomach but rather is released in the intestines. One of the active ingredients may also be coated with a sustained-release material which effects a sustained-release throughout the gastrointestinal tract and also serves to 10 minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the 15 formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a lowviscosity grade of hydroxypropyl methylcellulose (HPMC) or other 20 appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

These as well as other ways of minimizing 25 contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to those skilled in the art, once armed with 30 the present disclosure.

The present invention also includes pharmaceutical kits useful, for example, in the inhibition of platelet aggregation, the treatment of blood clots, and/or the 35 treatment of thromboembolic disorders, which comprise one or more containers containing a pharmaceutical

282

composition comprising a therapeutically effective amount of a compound of Formula I. Such kits may further include, if desired, one or more of various conventional pharmaceutical kit components, such as, for example, containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, may also be included in the kit.

In the present disclosure it should be understood that the specified materials and conditions are important in practicing the invention but that unspecified materials and conditions are not excluded so long as they do not prevent the benefits of the invention from being realized.

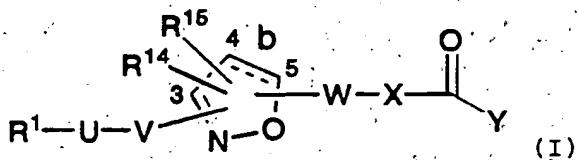
CLAIMS

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WHAT IS CLAIMED IS:

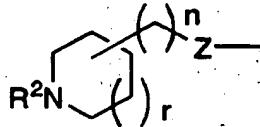
1. A compound of Formula I:

10



or pharmaceutically acceptable salt form thereof
wherein:

15 b is a single or double bond;

R¹ is selected from $R^2(R^3)N(CH_2)_qZ^-$, $R^2(R^3)N(R^2N=)CN(R^2)(CH_2)_qZ^-$, piperazinyl- $(CH_2)_qZ^-$ or

20

Z is selected from O, S, S(=O), or S(=O)₂;

25 R^2 and R^3 are independently selected from: H, C₁-C₁₀ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, C₆-C₁₀ aryl, C₇-C₁₁ arylalkyl, C₂-C₇ alkylcarbonyl, C₆-C₁₀ arylcarbonyl, C₂-C₁₀ alkoxy carbonyl, C₄-C₁₁ cycloalkoxy carbonyl, C₇-C₁₁ bicycloalkoxy carbonyl, C₆-C₁₀ aryloxycarbonyl, aryl(C₁-C₁₀ alkoxy) carbonyl, C₁-C₆ alkylcarbonyloxy(C₁-C₄ alkoxy) carbonyl, C₆-C₁₀

arylcarbonyloxy(C₁-C₄ alkoxy)carbonyl, C₄-C₁₁ cycloalkylcarbonyloxy(C₁-C₄ alkoxy)carbonyl;

U is selected from:

5 a single bond,
-(C₁-C₇ alkyl)-,
-(C₂-C₇ alkenyl)-,
-(C₂-C₇ alkynyl)-,
-(aryl)- substituted with 0-3 R^{6a}, or
10 -(pyridyl)- substituted with 0-3 R^{6a};

V is selected from:

a single bond;
-(C₁-C₇ alkyl)-, substituted with 0-3 groups
15 independently selected from R⁶ or R⁷;
-(C₂-C₇ alkenyl)-, substituted with 0-3 groups
independently selected from R⁶ or R⁷;
-(C₂-C₇ alkynyl)-, substituted with 0-2 groups
independently selected from R⁶ or R⁷;
20 -(aryl)-, substituted with 0-2 groups
independently selected from R⁶ or R⁷;
-(pyridyl)-, substituted with 0-2 groups
independently selected from R⁶ or R⁷; or
-(pyridazinyl)-, substituted with 0-2 groups
25 independently selected from R⁶ or R⁷;

W is selected from:

a single bond,
-(C₁-C₇ alkyl)-,
30 -(C₂-C₇ alkenyl)-,
-(C₂-C₇ alkynyl)-, or
-(C(R⁵)₂)_nC(=O)N(R^{5a})-;

X is selected from:

35 a single bond;

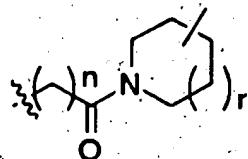
-(C₁-C₇ alkyl)-, substituted with 0-3 groups independently selected from R⁴, R⁸ or R¹⁴;

-(C₂-C₇ alkenyl)-, substituted with 0-3 groups

5

independently selected from R⁴, R⁸ or R¹⁴;

-(C₂-C₇ alkynyl)-, substituted with 0-2 groups independently selected from R⁴, R⁸ or R¹⁴; or



10 Y is selected from hydroxy, C₁ to C₁₀ alkyloxy, C₃ to C₁₁ cycloalkyloxy, C₆ to C₁₀ aryloxy, C₇ to C₁₁ aralkyloxy, C₃ to C₁₀ alkylcarbonyloxyalkyloxy, C₃ to C₁₀ alkoxy carbonyloxyalkyloxy, C₂ to C₁₀ alkoxy carbonylalkyloxy, C₅ to C₁₀ cycloalkylcarbonyloxyalkyloxy, C₅ to C₁₀ cycloalkoxycarbonyloxyalkyloxy, C₅ to C₁₀ cycloalkoxycarbonylalkyloxy, C₇ to C₁₁ aryloxycarbonylalkyloxy, C₈ to C₁₂ aryloxycarbonyloxyalkyloxy, C₈ to C₁₂ 20 arylcarbonyloxyalkyloxy, C₅ to C₁₀ alkoxyalkylcarbonyloxyalkyloxy, C₅ to C₁₀ (5-alkyl-1,3-dioxa-cyclopenten-2-one-yl)methoxy, C₁₀ to C₁₄ (5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methoxy; or (R²)(R³)N-(C₁-C₁₀ alkoxy)-;

25

R⁴ and R^{4b} are independently selected from H, C₁-C₁₀ alkyl, hydroxy, C₁-C₁₀ alkoxy, nitro, C₁-C₁₀ alkylcarbonyl; or -N(R¹²)R¹³;

30 R⁵ is selected from H, C₁-C₈ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylmethyl, C₆-C₁₀ aryl, C₇-C₁₁ arylalkyl, or C₁-C₁₀ alkyl substituted with 0-2 R^{4b};

5 R^{5a} is selected from hydrogen, hydroxy, C_1 to C_8 alkyl, C_2 to C_6 alkenyl, C_3 to C_{11} cycloalkyl, C_4 to C_{11} cycloalkylmethyl, C_1 - C_6 alkoxy, benzyloxy, C_6 to C_{10} aryl, heteroaryl, heteroarylalkyl, C_7 to C_{11} arylalkyl, adamantlylmethyl or C_1 - C_{10} alkyl substituted with 0-2 R^{4b} ;

10 alternately, R^5 and R^{5a} can be taken together to be 3-azabicyclononyl, 1-piperidinyl, 1-morpholinyl or 1-piperazinyl, each being optionally substituted with C_1 - C_6 alkyl, C_6 - C_{10} aryl, heteroaryl, C_7 - C_{11} arylalkyl, C_1 - C_6 alkylcarbonyl, C_3 - C_7 cycloalkylcarbonyl, C_1 - C_6 alkoxy carbonyl, C_7 - C_{11} arylalkoxycarbonyl, C_1 - C_6 alkylsulfonyl or C_6 - C_{10} arylsulfonyl;

15 R^{5b} is selected from C_1 - C_8 alkyl, C_2 - C_6 alkenyl, C_3 - C_{11} cycloalkyl, C_4 - C_{11} cycloalkylmethyl, C_6 - C_{10} aryl, C_7 - C_{11} arylalkyl, or C_1 - C_{10} alkyl substituted with 0-2 R^{4b} ;

20 R^6 is selected from H, C_1 - C_{10} alkyl, hydroxy, C_1 - C_{10} alkoxy, nitro, C_1 - C_{10} alkylcarbonyl, $-N(R^{12})R^{13}$, cyano, halo, CF_3 , CHO , CO_2R^5 , $C(=O)R^{5a}$, $CONR^{5a}R^{5a}$, $OC(=O)R^{5a}$, $OC(=O)OR^{5b}$, OR^{5a} , $OC(=O)NR^{5a}R^{5a}$, $OCH_2CO_2R^5$, $CO_2CH_2CO_2R^5$, NO_2 , $NR^{5a}C(=O)R^{5a}$, $NR^{5a}C(=O)OR^{5b}$, $NR^{5a}C(=O)NR^{5a}R^{5a}$, $NR^{5a}SO_2NR^{5a}R^{5a}$, $NR^{5a}SO_2R^5$, $S(O)pR^{5a}$, $SO_2NR^{5a}R^{5a}$, C_2 to C_6 alkenyl, C_3 to C_{11} cycloalkyl, C_4 to C_{11} cycloalkylmethyl;

25 C_6 to C_{10} aryl optionally substituted with 1-3 groups selected from halogen, C_1 - C_6 alkoxy, C_1 - C_6 alkyl, CF_3 , $S(O)_mMe$, or $-NMe_2$;

30

35

C₇ to C₁₁ arylalkyl, said aryl being optionally substituted with 1-3 groups selected from halogen, C₁-C₆ alkoxy, C₁-C₆ alkyl, CF₃, S(O)_mMe, or -NMe₂;

5 methylenedioxy when R⁶ is a substituent on aryl; or
a 5-10 membered heterocyclic ring containing 1-3 N,
O, or S heteroatoms, wherein said heterocyclic ring
may be saturated, partially saturated, or
10 fully unsaturated, said heterocyclic ring
being substituted with 0-2 R⁷;

R^{6a} is selected from C₁-C₄ alkyl, C₁-C₄ alkoxy, halo,
CF₃, NO₂, or NR¹²R¹³;

15 R⁷ is selected from H, C₁-C₁₀ alkyl, hydroxy, C₁-C₁₀ alkoxy, nitro, C₁-C₁₀ alkylcarbonyl, -N(R¹²)R¹³,
cyano, halo, CF₃, CHO, CO₂R⁵, C(=O)R^{5a}, CONR⁵R^{5a},
OC(=O)R^{5a}, OC(=O)OR^{5b}, OR^{5a}, OC(=O)NR⁵R^{5a}, OCH₂CO₂R⁵,
20 CO₂CH₂CO₂R⁵, NO₂, NR^{5a}C(=O)R^{5a}, NR^{5a}C(=O)OR^{5b},
NR^{5a}C(=O)NR^{5a}, NR^{5a}SO₂NR^{5a}, NR^{5a}SO₂R⁵, S(O)_pR^{5a},
SO₂NR^{5a}, C₂ to C₆ alkenyl, C₃ to C₁₁ cycloalkyl,
C₄ to C₁₁ cycloalkylmethyl, C₆ to C₁₀ aryl, or C₇ to
C₁₁ arylalkyl;

25 R⁸ is selected from:
H;
R⁶;
C₁-C₁₀ alkyl, substituted with 0-3 R⁶;
30 C₂-C₁₀ alkenyl, substituted with 0-3 R⁶;
C₂-C₁₀ alkynyl, substituted with 0-3 R⁶;
C₃-C₈ cycloalkyl, substituted with 0-3 R⁶;
C₅-C₆ cycloalkenyl, substituted with 0-2 R⁶;
aryl, substituted with 0-2 R⁶;

5-10 membered heterocyclic ring containing 1-3 N, 10
O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-2 R⁶;

5 R¹² and R¹³ are independently H, C₁-C₁₀ alkyl, C₁-C₁₀ alkoxy carbonyl, C₁-C₁₀ alkyl carbonyl, C₁-C₁₀ alkylsulfonyl, aryl(C₁-C₁₀ alkyl)sulfonyl, 10 arylsulfonyl, aryl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, C₇-C₁₁ arylalkyl, C₂-C₇ alkyl carbonyl, C₇-C₁₁ aryl carbonyl, C₂-C₁₀ alkoxy carbonyl, C₄-C₁₁ cycloalkoxy carbonyl, C₇-C₁₁ 15 bicycloalkoxy carbonyl, C₇-C₁₁ aryloxy carbonyl, heteroaryl carbonyl, heteroarylalkyl carbonyl or aryl(C₁-C₁₀ alkoxy) carbonyl;

20 R¹⁴ is selected from H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, aryl, heteroaryl or C₁-C₁₀ alkoxy carbonyl, CO₂R⁵ or -C(=O)N(R⁵)R^{5a};

25 R¹⁵ is selected from:

H;
R⁶;
C₁-C₁₀ alkyl, substituted with 0-8 R⁶;
C₂-C₁₀ alkenyl, substituted with 0-6 R⁶;
C₁-C₁₀ alkoxy, substituted with 0-6 R⁶;
aryl, substituted with 0-5 R⁶;
30 5-6 membered heterocyclic ring containing 1-2 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-5 R⁶;
35 C₁-C₁₀ alkoxy carbonyl substituted with 0-8 R⁶;
CO₂R⁵; or

-C(=O)N(R⁵)R^{5a};

provided that when b is a double bond, only one of R¹⁴ or R¹⁵ is present;

5

n is 0-4;

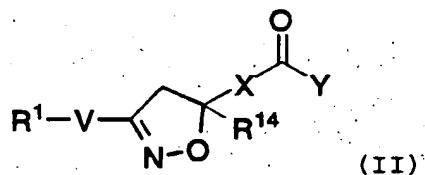
q is 2-7;

r is 0-3;

provided that n, q, and r are chosen such that the 10 number of in-chain atoms between R¹ and Y is in the range of 8-18.

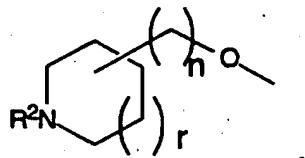
2. A compound of Claim 1 of Formula III:

15



wherein:

R¹ is selected from R²HN(CH₂)_qO-, 20 R²HN(R²N=)CNH(CH₂)_qO-, piperazinyl-(CH₂)_qO-, or



R² is selected from H, aryl(C₁-C₁₀ alkoxy)carbonyl, 25 C₁-C₁₀ alkoxy carbonyl;

R⁸ is selected from H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₃-C₈ cycloalkyl, C₅-C₆ cycloalkenyl, aryl, 5-6 membered heterocyclic ring containing 1-2 N, O, or S heteroatoms, wherein said heterocyclic ring may

290

be saturated, partially saturated, or fully unsaturated;

5 R⁶ and R⁷ are selected from H, C₁-C₁₀ alkyl, hydroxy, C₁-C₁₀ alkoxy, nitro, C₁-C₁₀ alkylcarbonyl, -N(R¹²)R¹³, cyano, or halo.

3. A compound of Claim 2 wherein:

10 X is selected from:

a single bond;

-(C₁-C₇ alkyl)-, substituted with 0-2 groups

independently selected from R⁴, R⁸ or R¹⁴;

-(C₂-C₇ alkenyl)-, substituted with 0-2 groups

15 independently selected from R⁴, R⁸ or R¹⁴;

-(C₂-C₇ alkynyl)-, substituted with 0-2 groups

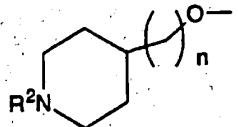
independently selected from R⁴, R⁸ or R¹⁴;

20 R⁸ is selected from H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₃-C₈ cycloalkyl, C₅-C₆ cycloalkenyl, aryl, 5-6 membered heterocyclic ring containing 1-2 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated.

25

4. A compound of Claim 2 wherein:

R¹ is



30

V is phenylene or pyridylene;

n is 1 or 2;

291

X is -(C₁-C₂)alkyl- substituted with 0-2 R⁴

Y is selected from:

5 hydroxy;
C₁ to C₁₀ alkoxy;
methylcarbonyloxymethoxy-;
ethylcarbonyloxymethoxy-;
t-butylcarbonyloxymethoxy-;

10 cyclohexylcarbonyloxymethoxy-;
1-(methylcarbonyloxy)ethoxy-;
1-(ethylcarbonyloxy)ethoxy-;
1-(t-butylcarbonyloxy)ethoxy-;
1-(cyclohexylcarbonyloxy)ethoxy-;

15 i-propyloxycarbonyloxymethoxy-;
t-butyloxycarbonyloxymethoxy-;
1-(i-propyloxycarbonyloxy)ethoxy-;
1-(cyclohexyloxycarbonyloxy)ethoxy-;
1-(t-butyloxycarbonyloxy)ethoxy-;

20 dimethylaminoethoxy-;
diethylaminoethoxy-;
(5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;
(5-(t-butyl)-1,3-dioxacyclopenten-2-on-4-
yl)methoxy-;

25 (1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methoxy-;
1-(2-(2-methoxypropyl)carbonyloxy)ethoxy-;

R⁴ is -NR¹²R¹³;

30 R¹² is H, C₁-C₄ alkoxy carbonyl, C₁-C₄ alkyl carbonyl,
C₁-C₄ alkylsulfonyl, arylalkylsulfonyl,
arylsulfonyl, benzyl, benzoyl, phenoxy carbonyl,
benzyloxycarbonyl, arylalkylsulfonyl,
pyridyl carbonyl, or pyridylmethyl carbonyl;

35

R¹³ is H.

292

5. A compound of Claim 1, or a pharmaceutically acceptable salt form thereof, selected from:

5 $5(R,S)$ -3-[(4-(2-piperidin-4-yl)ethoxyphenyl]isoxazolin-5-yl]acetic acid;

5 $5(R,S)$ -N-(butanesulfonyl)-L-{3-[4-(2-piperidin-4-yl)ethoxyphenyl]isoxazolin-5-yl}glycine;

5 $5(R,S)$ -N-(α -toluenesulfonyl)-L-{3-[4-(2-piperidin-4-yl)ethoxyphenyl]isoxazolin-5-yl}glycine;

10 5 $5(R,S)$ -N-[(benzyloxy)carbonyl]-L-{3-[4-(2-piperidin-4-yl)ethoxyphenyl]isoxazolin-5-yl}glycine;

5 $5(R,S)$ -N-(pentanoyl)-L-{3-[4-(2-piperidin-4-yl)ethoxyphenyl]isoxazolin-5-yl}glycine;

15 5 $5(R,S)$ -3-[(4-(piperidin-4-yl)methoxyphenyl]isoxazolin-5-yl]propanoic acid;

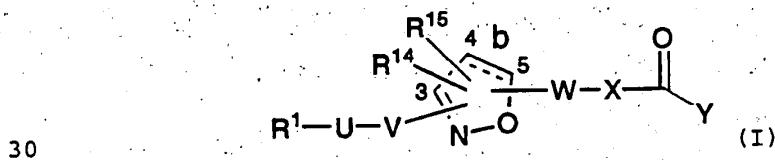
2 $2(R,S)$ -5 $5(R,S)$ -N-(butanesulfonyl)amino-{3-[4-(piperidin-4-yl)methoxyphenyl]isoxazolin-5-yl}propanoic acid;

2 $2(R,S)$ -5 $5(R,S)$ -N-(α -toluenesulfonyl)amino-{3-[4-(piperidin-4-yl)methoxyphenyl]isoxazolin-5-yl}propanoic acid;

20 2 $2(R,S)$ -5 $5(R,S)$ -N-[(benzyloxy)carbonyl]amino-{3-[4-(piperidin-4-yl)methoxyphenyl]isoxazolin-5-yl}propanoic acid;

25 2 $2(R,S)$ -5 $5(R,S)$ -N-(pentanoyl)amino-{3-[4-(piperidin-4-yl)methoxyphenyl]isoxazolin-5-yl}propanoic acid.

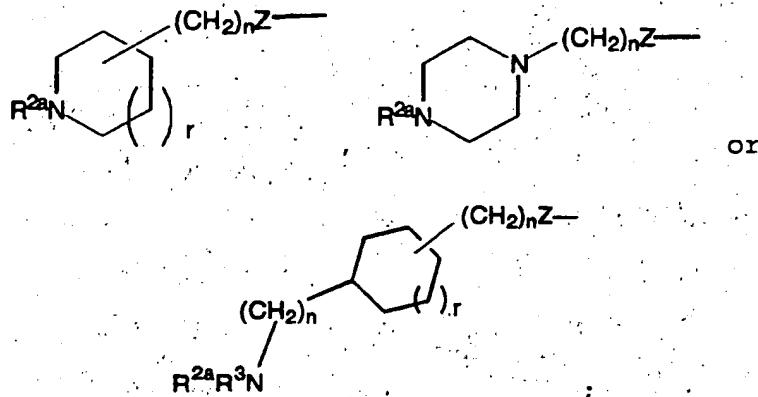
6. A compound of Formula I:



or a pharmaceutically acceptable salt form thereof
wherein:

b is a single or double bond;

10 R¹ is selected from R^{2a}(R³)N-, R²(R³)N(R²N=)C-,
 15 R^{2a}(R³)N(CH₂)_qZ-, R²(R³)N(R²N=)C(CH₂)_qZ-,
 R²(R³)N(R²N=)CN(R²)-,



20 Z is selected from: a bond, O, S, S(=O), S(=O)₂;

25 R² and R³ are independently selected from: H, C₁-C₁₀
 alkyl, C₃-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁
 cycloalkylalkyl, C₆-C₁₀ aryl, C₇-C₁₁ arylalkyl, C₂-C₇
 alkylcarbonyl, C₇-C₁₁ arylcarbonyl, C₂-C₁₀
 alkoxy carbonyl, C₄-C₁₁ cycloalkoxy carbonyl, C₇-C₁₁
 bicycloalkoxy carbonyl, C₇-C₁₁ aryloxy carbonyl,
 aryl(C₁-C₁₀ alkoxy) carbonyl, C₁-C₆
 alkylcarbonyloxy(C₁-C₄ alkoxy) carbonyl, C₆-C₁₀
 arylcarbonyloxy(C₁-C₄ alkoxy) carbonyl, C₄-C₁₁
 cycloalkylcarbonyloxy(C₁-C₄ alkoxy) carbonyl;

30 R^{2a} is R² or R²(R³)N(R²N=)C-;

35 U is selected from:

a single bond,
 -(C₁-C₇ alkyl)-,

294

- (C₂-C₇ alkenyl)-,
- (C₂-C₇ alkynyl)-,
- (aryl)- substituted with 0-3 R^{6a}, or
- (pyridyl)- substituted with 0-3 R^{6a};

5

v is selected from:

- a single bond;
- (C₁-C₇ alkyl)-, substituted with 0-3 groups independently selected from R⁶ or R⁷;
- (C₂-C₇ alkenyl)-, substituted with 0-3 groups independently selected from R⁶ or R⁷;
- (C₂-C₇ alkynyl)-, substituted with 0-3 groups independently selected from R⁶ or R⁷;
- (phenyl)-Q-, said phenyl substituted with 0-2 groups independently selected from R⁶ or R⁷;
- (pyridyl)-Q-, said pyridyl substituted with 0-2 groups independently selected from R⁶ or R⁷; or
- (pyridazinyl)-Q-, said pyridazinyl substituted with 0-2 groups independently selected from R⁶ or R⁷;

15

20

Q is selected from

- a single bond,
- O-, -S(O)_m-, -N(R¹²)-, -(CH₂)_m-, -C(=O)-,
- N(R^{5a})C(=O)-, -C(=O)N(R^{5a})-, -CH₂O-, -OCH₂-,
- CH₂N(R¹²)-, -N(R¹²)CH₂-, -CH₂C(=O)-, -C(=O)CH₂-,
- CH₂S(O)_m-, or -S(O)_mCH₂-,

25

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provided that when b is a single bond, and R¹-U-V is a substituent on C5 of the central 5-membered ring of Formula I, then Q is not -O-, -S(O)_m-, -N(R¹²)-, -C(=O)N(R^{5a})-, -CH₂O-, CH₂N(R¹²)- or -CH₂S(O)_m-;

w is selected from:

- (C(R⁴)₂)_nC(=O)N(R^{5a}) - , or
-C(=O)-N(R^{5a})-(C(R⁴)₂)_n- ;

X is selected from:

5 a single bond,
- (C(R⁴)₂)_n-C(R⁴)(R⁸)-C(R⁴)(R^{4a}) - , with the proviso
that when n is 0 or 1, then at least one of R^{4a} or
R⁸ is other than H or methyl;

10 Y is selected from hydroxy, C₁ to C₁₀ alkyloxy, C₃ to
C₁₁ cycloalkyloxy, C₆ to C₁₀ aryloxy, C₇ to C₁₁
aralkyloxy, C₃ to C₁₀ alkylcarbonyloxyalkyloxy, C₃
to C₁₀ alkoxy carbonyloxyalkyloxy, C₂ to C₁₀
alkoxycarbonylalkyloxy, C₅ to C₁₀
15 cycloalkylcarbonyloxyalkyloxy, C₅ to C₁₀
cycloalkoxycarbonyloxyalkyloxy, C₅ to C₁₀
cycloalkoxycarbonylalkyloxy, C₇ to C₁₁
aryloxycarbonylalkyloxy, C₈ to C₁₂
aryloxy carbonyloxyalkyloxy, C₈ to C₁₂
20 arylcarbonyloxyalkyloxy, C₅ to C₁₀
alkoxyalkylcarbonyloxyalkyloxy, C₅ to C₁₀ (5-alkyl-
1,3-dioxa-cyclopenten-2-one-yl)methyloxy, C₁₀ to C₁₄
(5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy,
(R²)(R³)N-(C₁-C₁₀ alkoxy) - ;

25 R⁴ is selected from H, C₁-C₁₀ alkyl, C₁-C₁₀
alkylcarbonyl, aryl, arylalkyl, cycloalkyl, or
cycloalkylalkyl;

30 alternately, two R⁴ groups on adjacent carbon atoms may
join to form a bond thereby to form a carbon-carbon
double or triple bond between such adjacent carbon
atoms;

5 R^{4a} is selected from H, hydroxy, C_1 - C_{10} alkoxy, nitro, $N(R^5)R^{5a}$, $-N(R^{12})R^{13}$, $-N(R^{16})R^{17}$, C_1 - C_{10} alkyl substituted with 0-3 R^6 , aryl substituted with 0-3 R^6 , or C_1 - C_{10} alkylcarbonyl;

10 R^{4b} is selected from H, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_7 cycloalkyl, C_7 - C_{14} bicycloalkyl, hydroxy, C_1 - C_6 alkoxy, C_1 - C_6 alkylthio, C_1 - C_6 alkylsulfinyl, C_1 - C_6 alkylsulfonyl, nitro, C_1 - C_6 alkylcarbonyl, C_6 - C_{10} aryl, $-N(R^{12})R^{13}$, halo, CF_3 , CN , C_1 - C_6 alkoxy carbonyl, carboxy, piperidinyl, morpholinyl or pyridinyl;

15 15 R^5 is selected from H, C_1 - C_8 alkyl, C_3 - C_6 alkenyl, C_3 - C_{11} cycloalkyl, C_4 - C_{11} cycloalkylmethyl, C_6 - C_{10} aryl, C_7 - C_{11} arylalkyl, or C_1 - C_{10} alkyl substituted with 0-2 R^{4b} ;

20 20 R^{5a} is selected from hydrogen, hydroxy, C_1 to C_8 alkyl, C_3 - C_6 alkenyl, C_3 to C_{11} cycloalkyl, C_4 to C_{11} cycloalkylmethyl, C_1 - C_6 alkoxy, benzyloxy, C_6 to C_{10} aryl, heteroaryl, heteroarylalkyl, C_7 to C_{11} arylalkyl, adamantylmethyl, or C_1 - C_{10} alkyl substituted with 0-2 R^{4b} ;

25 30 alternately, R^5 and R^{5a} when both are substituents on the same nitrogen atom (as in $-NR^5R^{5a}$) can be taken together with the nitrogen atom to which they are attached to form 3-azabicyclononyl, 1,2,3,4-tetrahydro-1-quinolinyl, 1,2,3,4-tetrahydro-2-isoquinolinyl, 1-piperidinyl, 1-morpholinyl, 1-pyrrolidinyl, thiamorpholinyl, thiazolidinyl or 1-piperazinyl, each being optionally substituted with C_1 - C_6 alkyl, C_6 - C_{10} aryl, heteroaryl, C_7 - C_{11}

arylalkyl, C₁-C₆ alkylcarbonyl, C₃-C₇
cycloalkylcarbonyl, C₁-C₆ alkoxy carbonyl, C₇-C₁₁
arylalkoxycarbonyl, C₁-C₆ alkylsulfonyl or C₆-C₁₀
arylsulfonyl;

5

R^{5b} is selected from C₁-C₈ alkyl, C₂-C₆ alkenyl, C₃-C₁₁
cycloalkyl, C₄-C₁₁ cycloalkylmethyl, C₆-C₁₀ aryl,
C₇-C₁₁ arylalkyl, or C₁-C₁₀ alkyl substituted with
0-2 R^{4b};

10

R⁶ is selected from H, C₁-C₁₀ alkyl, hydroxy, C₁-C₁₀
alkoxy, nitro, C₁-C₁₀ alkylcarbonyl, -N(R¹²)R¹³,
cyano, halo, CF₃, CHO, CO₂R⁵, C(=O)R^{5a}, CONR⁵R^{5a},
OC(=O)R^{5a}, OC(=O)OR^{5b}, OR^{5a}, OC(=O)NR⁵R^{5a}, OCH₂CO₂R⁵,
CO₂CH₂CO₂R⁵, NO₂, NR^{5a}C(=O)R^{5a}, NR^{5a}C(=O)OR^{5b},
NR^{5a}C(=O)NR⁵R^{5a}, NR^{5a}SO₂NR⁵R^{5a}, NR^{5a}SO₂R⁵, S(O)R^{5a},
SO₂NR⁵R^{5a}, SiMe₃, C₂ to C₆ alkenyl, C₃ to C₁₁
cycloalkyl, C₄ to C₁₁ cycloalkylmethyl;

20

C₆ to C₁₀ aryl optionally substituted with 1-3
groups selected from halogen, C₁-C₆ alkoxy, C₁-C₆
alkyl, CF₃, S(O)_mMe, or -NMe₂;

25

C₇ to C₁₁ arylalkyl, said aryl being optionally
substituted with 1-3 groups selected from halogen,
C₁-C₆ alkoxy, C₁-C₆ alkyl, CF₃, S(O)_mMe, or -NMe₂;

30

methylenedioxy when R⁶ is a substituent on aryl; or
a 5-10 membered heterocyclic ring containing 1-3 N,
O, or S heteroatoms, wherein said heterocyclic
ring may be saturated, partially saturated, or
fully unsaturated, said heterocyclic ring
being substituted with 0-2 R⁷;

35

R^{6a} is selected from C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, CF₃, NO₂, or NR¹²R¹³;

R⁷ is selected from H, C₁-C₁₀ alkyl, hydroxy, C₁-C₁₀ alkoxy, nitro, C₁-C₁₀ alkylcarbonyl, -N(R¹²)R¹³, cyano, halo, CF₃, CHO, CO₂R⁵, C(=O)R^{5a}, CONR⁵R^{5a}, OC(=O)R^{5a}, OC(=O)OR^{5b}, OR^{5a}, OC(=O)NR⁵R^{5a}, OCH₂CO₂R⁵, CO₂CH₂CO₂R⁵, NO₂, NR^{5a}C(=O)R^{5a}, NR^{5a}C(=O)OR^{5b}, NR^{5a}C(=O)NR⁵R^{5a}, NR^{5a}SO₂NR⁵R^{5a}, NR^{5a}SO₂R⁵, S(O)pR^{5a}, SO₂NR⁵R^{5a}, C₂ to C₆ alkenyl, C₃ to C₁₁ cycloalkyl, C₄ to C₁₁ cycloalkylmethyl, C₆ to C₁₀ aryl, or C₇ to C₁₁ arylalkyl;

R⁸ is selected from:

R⁶;

C₁-C₁₀ alkyl, substituted with 0-3 R⁶;

C₂-C₁₀ alkenyl, substituted with 0-3 R⁶;

C₂-C₁₀ alkynyl, substituted with 0-3 R⁶;

C₃-C₈ cycloalkyl, substituted with 0-3 R⁶;

C₅-C₆ cycloalkenyl, substituted with 0-3 R⁶;

aryl, substituted with 0-3 R⁶;

5-10 membered heterocyclic ring containing 1-3 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-2 R⁶;

R¹² and R¹³ are independently H, C₁-C₁₀ alkyl, C₁-C₁₀ alkoxy carbonyl, C₁-C₁₀ alkyl carbonyl, C₁-C₁₀ alkylsulfonyl, aryl(C₁-C₁₀ alkyl)sulfonyl, arylsulfonyl, aryl(C₂-C₁₀ alkenyl)sulfonyl, heteroarylsulfonyl, aryl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, C₇-C₁₁ arylalkyl, C₇-C₁₁ aryl carbonyl, C₄-C₁₁ cycloalkoxycarbonyl, C₇-C₁₁ bicycloalkoxycarbonyl, C₇-C₁₁ aryloxycarbonyl,

heteroarylcarbonyl, heteroarylalkylcarbonyl, or
aryl(C₁-C₁₀ alkoxy)carbonyl, wherein said aryls are
optionally substituted with 0-3 substituents
selected from the group consisting of: C₁-C₄ alkyl,
C₁-C₄ alkoxy, halo, CF₃, and NO₂;

5 R¹⁴ is selected from H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl,
C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, aryl, heteroaryl or
C₁-C₁₀ alkoxy carbonyl, CO₂R⁵ or -C(=O)N(R⁵)R^{5a},

10

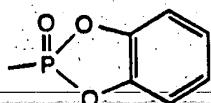
R¹⁵ is selected from:
H; R⁶; -CO₂R⁵; -C(=O)N(R⁵)R^{5a};
C₁-C₁₀ alkoxy carbonyl substituted with 0-2 R⁶;
C₁-C₁₀ alkyl, substituted with 0-3 R⁶;
15 C₂-C₁₀ alkenyl, substituted with 0-3 R⁶;
C₁-C₁₀ alkoxy, substituted with 0-3 R⁶;
aryl, substituted with 0-3 R⁶; or
5-10 membered heterocyclic ring containing 1-3 N,
O, or S heteroatoms, wherein said heterocyclic
20 ring may be saturated, partially saturated, or
fully unsaturated, said heterocyclic ring
being substituted with 0-2 R⁶;

provided that when b is a double bond, only one of R¹⁴
25 or R¹⁵ is present;

R¹⁶ is selected from:
-C(=O)-O-R^{18a},
-C(=O)-R^{18b},
30 -C(=O)N(R^{18b})₂,
-C(=O)NH₂SO₂R^{18a},
-C(=O)NHC(=O)R^{18b},
-C(=O)NHC(=O)OR^{18a},
-C(=O)NHSO₂NHR^{18b},
35 -C(=O)-NH-R^{18b},

300

- NH-C(=O)-O-R^{18a},
- NH-C(=O)-R^{18b},
- NH-C(=O)-NH-R^{18b},
- SO₂-O-R^{18a},
- 5 -SO₂-R^{18a},
- SO₂-N(R^{18b})₂,
- SO₂-NHC(=O)O-R^{18b},
- P(=S)(OR^{18a})₂,
- P(=O)(OR^{18a})₂,
- 10 -P(=S)(R^{18a})₂,
- P(=O)(R^{18a})₂, or



R¹⁷ is selected from: H, C₁-C₁₀ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₅ cycloalkylalkyl, aryl, aryl(C₁-C₁₀ alkyl)-;

15

R^{18a} is selected from:

20 C₁-C₈ alkyl substituted with 0-2 R¹⁹,

C₂-C₈ alkenyl substituted with 0-2 R¹⁹,

C₂-C₈ alkynyl substituted with 0-2 R¹⁹,

C₃-C₈ cycloalkyl substituted with 0-2 R¹⁹,

aryl substituted with 0-4 R¹⁹,

aryl(C₁-C₆ alkyl)- substituted with 0-4 R¹⁹,

25

a 5-10 membered heterocyclic ring system having 1-3 heteroatoms selected independently from O, S, and N, said heterocyclic ring being substituted with 0-4 R¹⁹,

30

C₁-C₆ alkyl substituted with a 5-10 membered heterocyclic ring system having 1-3 heteroatoms selected independently from O, S, and N, said heterocyclic ring being substituted with 0-4 R¹⁹;

R^{18b} is selected from R^{18a} or H;

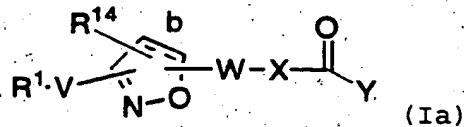
R¹⁹ is selected from H, halogen, CF₃, CN, NO₂, NR¹²R¹³,
 5 C₁-C₈ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl, aryl(C₁-C₆ alkyl)-, C₁-C₆ alkoxy, or C₁-C₄ alkoxycarbonyl;

n is 0-4;
 10 q is 1-7;
 r is 0-3;

provided that n, q and r are chosen such that the number of in-chain atoms connecting R¹ and Y is in the range of 8-18.

15

7. A compound of Claim 6 of Formula Ia:



wherein:
 20 Z is selected from a bond, O, or S;

R² is selected from H, aryl(C₁-C₁₀ alkoxy)carbonyl, or C₁-C₁₀ alkoxycarbonyl;

25 W is -(CH₂)_nC(=O)N(R^{5a})-;

X is -(C(R⁴)₂)_n-C(R⁴)(R⁸)-CH(R⁴)-, with the proviso that when n is 0 or 1, then at least one of R^{4a} or R⁸ is other than H or methyl;

30 R⁵ is selected from H or C₁-C₁₀ alkyl substituted with 0-6 R^{4b};

R^6 is selected from H; C₁-C₁₀ alkyl, hydroxy, C₁-C₁₀ alkoxy, nitro, C₁-C₁₀ alkylcarbonyl, -N(R¹²)R¹³, -NR⁵R^{5a}, CO₂R⁵, S(O)_mR⁵, OR⁵, cyano, halo;

5 C₆ to C₁₀ aryl optionally substituted with 1-3 groups selected from halogen, C₁-C₆ alkoxy, C₁-C₆ alkyl, CF₃, S(O)_mMe, or -NMe₂.

10 C₇ to C₁₁ arylalkyl, said aryl being optionally substituted with 1-3 groups selected from halogen, C₁-C₆ alkoxy, C₁-C₆ alkyl, CF₃, S(O)_mMe, or -NMe₂;

methylenedioxy when R^6 is a substituent on aryl; or

15 a 5-10 membered heterocyclic ring containing 1-3 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-2 R⁷;

20 R⁷ is selected from selected from H, C₁-C₁₀ alkyl, hydroxy, C₁-C₁₀ alkoxy, nitro, C₁-C₁₀ alkylcarbonyl, -N(R¹²)R¹³, cyano, or halo;

25 R⁸ is selected from:
 -CONR⁵NR^{5a}; -CO₂R⁵;
 C₁-C₁₀ alkyl, substituted with 0-3 R⁶;
 C₂-C₁₀ alkenyl, substituted with 0-3 R⁶;
 C₂-C₁₀ alkynyl, substituted with 0-3 R⁶;
 30 C₃-C₈ cycloalkyl, substituted with 0-3 R⁶;
 C₅-C₆ cycloalkenyl, substituted with 0-3 R⁶;
 aryl, substituted with 0-2 R⁶;
 35 a 5-10 membered heterocyclic ring containing 1-3 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or

303

fully unsaturated, said heterocyclic ring
being substituted with 0-2 R⁶;

5 R¹² and R¹³ are each independently selected from H,
C₁-C₁₀ alkyl, C₁-C₁₀ alkoxy carbonyl, C₁-C₁₀
alkyl carbonyl, C₁-C₁₀ alkylsulfonyl,
10 aryl(C₁-C₁₀ alkyl)sulfonyl, arylsulfonyl, aryl,
heteroaryl carbonyl, or heteroarylalkyl carbonyl,
wherein said aryls are optionally substituted with
15 0-3 substituents selected from the group consisting
of: C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, CF₃, and NO₂.

8. A compound of Claim 7 wherein:

15 Z is selected from a bond or O;

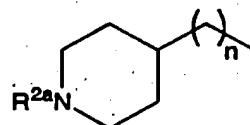
W is -(CH₂)_nC(=O)N(R¹²)-;

X is -C(R⁴)(R⁸)-C(R⁴)₂-.

20 9. A compound of Claim 7 wherein:

R¹ is R²NHC(=NR²)- or R²NHC(=NR²)NH- and V is phenylene
or pyridylene; or

25 R¹ is



and V is a single bond;

n is 1 or 2;

30 X is -CHR⁸CH₂-;

Y is selected from:

hydroxy;
C₁ to C₁₀ alkoxy;
methylcarbonyloxymethoxy-;
ethylcarbonyloxymethoxy-;
5 t-butyldcarbonyloxymethoxy-;
cyclohexylcarbonyloxymethoxy-;
1-(methylcarbonyloxy)ethoxy-;
1-(ethylcarbonyloxy)ethoxy-;
1-(t-butyldcarbonyloxy)ethoxy-;
10 1-(cyclohexylcarbonyloxy)ethoxy-;
i-propyloxycarbonyloxymethoxy-;
t-butyloxycarbonyloxymethoxy-;
1-(i-propyloxycarbonyloxy)ethoxy-;
1-(cyclohexyloxycarbonyloxy)ethoxy-;
15 1-(t-butyloxycarbonyloxy)ethoxy-;
dimethylaminoethoxy-;
diethylaminoethoxy-;
(5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;
(5-(t-butyl)-1,3-dioxacyclopenten-2-on-4-
20 yl)methoxy-;
(1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methoxy-;
1-(2-(2-methoxypropyl)carbonyloxy)ethoxy-;

R⁶ is selected from H, C₁-C₄ alkyl, hydroxy, C₁-C₄
25 alkoxy, nitro, C₁-C₁₀ alkylcarbonyl, -N(R¹²)R¹³,
-NR⁵R^{5a}, CO₂R⁵, S(O)_mR⁵, OR⁵, cyano, halo;

C₆ to C₁₀ aryl optionally substituted with 1-3
groups selected from halogen, C₁-C₆ alkoxy, C₁-C₆
30 alkyl, CF₃, S(O)_mMe, or -NMe₂;

methylenedioxy when R⁶ is a substituent on aryl; or
a heterocyclic ring system selected from pyridinyl,
35 furanyl, thiazolyl, thiienyl, pyrrolyl,
pyrazolyl, triazolyl, imidazolyl,

305

benzofuranyl, indolyl, indolinyl, quinolinyl,
isoquinolinyl, benzimidazolyl, piperidinyl,
tetrahydrofuranyl, pyranyl, pyridinyl, 3H-

5

indolyl, carbazolyl, pyrrolidinyl,
piperidinyl, indolinyl, isoxazolinyl or
morpholinyl;

R⁸ is selected from:

-CONR⁵NR^{5a}; -CO₂R⁵;

10

C₁-C₁₀ alkyl, substituted with 0-3 R⁶;

C₂-C₁₀ alkenyl, substituted with 0-3 R⁶;

C₂-C₁₀ alkynyl, substituted with 0-3 R⁶;

C₃-C₈ cycloalkyl, substituted with 0-3 R⁶;

aryl, substituted with 0-2 R⁶;

15

a heterocyclic ring system selected from pyridinyl,
furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl,
triazolyl, imidazolyl, benzofuranyl, indolyl,
indolinyl, quinolinyl, isoquinolinyl, isoxazolinyl,
benzimidazolyl, piperidinyl, tetrahydrofuranyl,
pyranyl, pyridinyl, 3H-indolyl, carbazolyl,
pyrrolidinyl, piperidinyl, indolinyl, or
morpholinyl, said heterocyclic ring being
substituted with 0-2 R⁶;

25

R¹² is selected from H, C₁-C₆ alkyl, C₁-C₄

alkoxycarbonyl, C₁-C₆ alkylcarbonyl, C₁-C₆

alkylsulfonyl, aryl(C₁-C₄ alkyl)sulfonyl,

arylsulfonyl, aryl, pyridylcarbonyl or

30

pyridylmethylcarbonyl, wherein said aryls are

optionally substituted with 0-3 substituents

selected from the group consisting of: C₁-C₄ alkyl,

C₁-C₄ alkoxy, halo, CF₃, and NO₂; and

35 R¹³ is H.

306

10. A compound of Claim 6, or a pharmaceutically acceptable salt form thereof, selected from:

3 (R,S) - {5 (R,S) - N - [3 - (4 - amidinophenyl) isoxazolin-5 -
5 yl acetyl] amino} - 3 - phenylpropanoic acid;

3 (R,S) - {5 (R,S) - N - [3 - (4 - amidinophenyl) isoxazolin-5 -
5 yl acetyl] amino} - pentanoic acid;

3 (R) - {5 (R,S) - N - [3 - (4 - amidinophenyl) isoxazolin-5 -
5 yl acetyl] amino} heptanoic acid;

10 3 (R,S) - {5 (R,S) - N - [3 - (4 - amidinophenyl) isoxazolin-5 -
5 yl acetyl] amino} - 4 - (phenylthio) butanoic acid;

3 (R,S) - {5 (R,S) - N - [3 - (4 - amidinophenyl) isoxazolin-5 -
5 yl acetyl] amino} - 4 - (phenylsulfonamido) butanoic acid;

3 (R,S) - {5 (R,S) - N - [3 - (4 - amidinophenyl) isoxazolin-5 -
15 5 yl acetyl] amino} - 4 - (n - butylsulfonamido) butanoic
acid;

3 (S) - {5 (R,S) - N - [3 - (4 - amidinophenyl) isoxazolin-5 -
5 yl acetyl] amino} - 3 -
(adamantylmethyldaminocarbonyl) propanoic acid;

20 3 (S) - {5 (R,S) - N - [3 - (4 - amidinophenyl) isoxazolin-5 -
5 yl acetyl] amino} - 3 - (1 -
azabicyclo [3.2.2] nonylcarbonyl) propanoic acid;

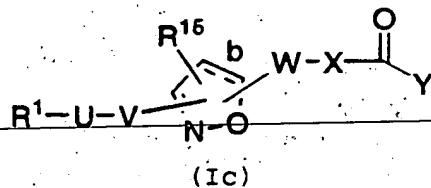
3 (S) - {5 (R,S) - N - [3 - (4 - amidinophenyl) isoxazolin-5 -
25 5 yl acetyl] amino} - 3 - (phenethylaminocarbonyl) propanoic
acid.

3 (R) - {5 (R,S) - N - [3 - (4 - amidinophenyl) isoxazolin-5 -
5 yl acetyl] amino} - 3 - (3 - pyridylethyl) propanoic acid.

3 (R) - {5 (R,S) - N - [3 - (4 - amidinophenyl) isoxazolin-5 -
5 yl acetyl] amino} - 3 - (2 - pyridylethyl) propanoic acid.

30 3 (R) - {5 (R,S) - N - [3 - (4 - amidinophenyl) isoxazolin-5 -
5 yl acetyl] amino} - 3 - (phenylpropyl) propanoic acid.

11. A compound of Claim 6 of Formula Ic:

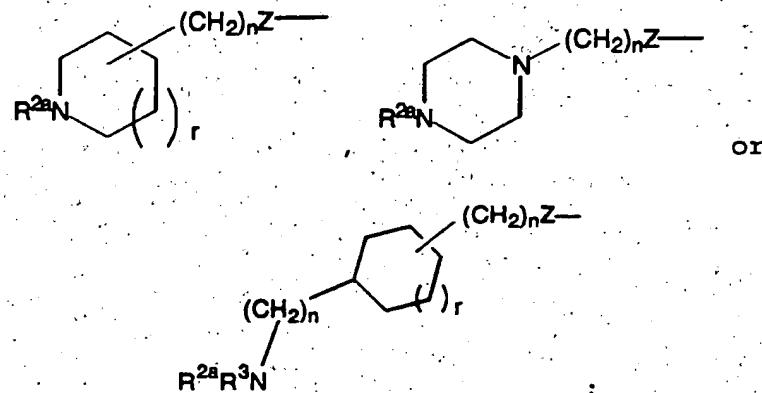


wherein:

5 b is a single or double bond;

10 R^1 is selected from $R^{2a}(R^3)N-$, $R^2(R^3)N(R^2N=)C-$,
 $R^{2a}(R^3)N(CH_2)_qZ-$, $R^2(R^3)N(R^2N=)C(CH_2)_qZ-$,
 $R^2(R^3)N(R^2N=)CN(R^2)-$,

15



15

Z is selected from a bond, O, or S;

20 R^2 and R^3 are independently selected from H, aryl(C_1-C_{10} alkoxy)carbonyl, or C_1-C_{10} alkoxy carbonyl;

25

R^{2a} is R^2 or $R^2(R^3)N(R^2N=)C$;

U is a single bond,

25 V is selected from:
a single bond;

- (C₁-C₇ alkyl) -, substituted with 0-3 groups
 independently selected from R⁶ or R⁷;
 - (C₂-C₇ alkenyl) -, substituted with 0-3 groups
 independently selected from R⁶ or R⁷;
 5 - (C₂-C₇ alkynyl) -, substituted with 0-3 groups
 independently selected from R⁶ or R⁷;
 - (phenyl)-Q-, said phenyl substituted with 0-2
 groups independently selected from R⁶ or R⁷;
 10 - (pyridyl)-Q-, said pyridyl substituted with 0-2
 groups independently selected from R⁶ or R⁷; or
 - (pyridazinyl)-Q-, said pyridazinyl substituted
 with 0-2 groups independently selected from R⁶
 or R⁷.

15 Q is selected from
 a single bond,
 -O-, -S(O)_m-, -N(R¹²)-, -(CH₂)_m-, -C(=O)-,
 -N(R^{5a})C(=O)-, -C(=O)N(R^{5a})-, -CH₂O-, -OCH₂-,
 20 -CH₂N(R¹²)-, -N(R¹²)CH₂-, -CH₂C(=O)-, -C(=O)CH₂-,
 -CH₂S(O)_m-, or -S(O)_mCH₂-,

provided that when b is a single bond, and R¹-U-V-
 is a substituent on C5 of the central 5-membered
 ring of Formula Ic, then Q is not -O-, -S(O)_m-,
 25 -N(R¹²)-, -C(=O)N(R^{5a})-, -CH₂O-, CH₂N(R¹²)- or
 -CH₂S(O)_m-

30 W is selected from:
 - (C(R⁴)₂)₂C(=O)-N(R^{5a})-, or
 -C(=O)-N(R^{5a})-(C(R⁴)₂)-;

X is -C(R⁴)₂-CHR^{4a}-;

10 R⁴ is selected from H, C₁-C₁₀ alkyl, C₁-C₁₀ alkylcarbonyl, aryl, arylalkyl, cycloalkyl, or cycloalkylalkyl;

15 R^{4a} is selected from hydroxy, C₁-C₁₀ alkoxy, nitro, -N(R⁵)R^{5a}, -N(R¹²)R¹³, or -N(R¹⁶)R¹⁷, C₁-C₁₀ alkyl substituted with 0-3 R⁶, aryl substituted with 0-3 R⁶, or C₁-C₁₀ alkylcarbonyl;

20 10 R^{4b} is selected from H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₆ alkylsulfinyl, C₁-C₆ alkylsulfonyl, nitro, C₁-C₆ alkylcarbonyl, C₆-C₁₀ aryl, -N(R¹²)R¹³, halo, 15 CF₃, CN, C₁-C₆ alkoxy carbonyl, carboxy, piperidinyl, morpholinyl or pyridyl;

25 R⁵ is selected from H or C₁-C₁₀ alkyl substituted with 0-6 R^{4b};

30 20 R^{5a} is selected from hydrogen, hydroxy, C₁ to C₈ alkyl, C₂ to C₆ alkenyl, C₃ to C₁₁ cycloalkyl, C₄ to C₁₁ cycloalkylmethyl, C₁-C₆ alkoxy, benzyloxy, C₆ to C₁₀ aryl, heteroaryl, heteroarylalkyl, C₇ to C₁₁ 25 arylalkyl, or adamantylmethyl, C₁-C₁₀ alkyl substituted with 0-2 R^{4b};

35 alternately, R⁵ and R^{5a} can be taken together to be 3-azabicyclononyl, 1,2,3,4-tetrahydro-1-quinolinyl, 1,2,3,4-tetrahydro-2-isoquinolinyl, 1-piperidinyl, 1-morpholinyl, 1-pyrrolidinyl, thiamorpholinyl, thiazolidinyl or 1-piperazinyl, each being optionally substituted with C₁-C₆ alkyl, C₆-C₁₀ aryl, heteroaryl, C₇-C₁₁ arylalkyl, C₁-C₆

310

alkylcarbonyl, C₃-C₇ cycloalkylcarbonyl, C₁-C₆ alkoxy carbonyl or C₇-C₁₁ arylalkoxycarbonyl;

5 R^{5b} is selected from C₁-C₈ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylmethyl, C₆-C₁₀ aryl, C₇-C₁₁ arylalkyl, or C₁-C₁₀ alkyl substituted with 0-2 R^{4b}.

10 Y is selected from hydroxy, C₁ to C₁₀ alkyloxy, C₃ to C₁₁ cycloalkyloxy, C₆ to C₁₀ aryloxy, C₇ to C₁₁ aralkyloxy, C₃ to C₁₀ alkylcarbonyloxyalkyloxy, C₃ to C₁₀ alkoxy carbonyloxyalkyloxy, C₂ to C₁₀ alkoxy carbonylalkyloxy, C₅ to C₁₀

15 cycloalkylcarbonyloxyalkyloxy, C₅ to C₁₀ cycloalkoxycarbonyloxyalkyloxy, C₅ to C₁₀ cycloalkoxycarbonylalkyloxy, C₇ to C₁₁ aryloxycarbonylalkyloxy, C₈ to C₁₂ aryloxycarbonyloxyalkyloxy, C₈ to C₁₂ arylcarbonyloxyalkyloxy, C₅ to C₁₀

20 alkoxyalkylcarbonyloxyalkyloxy, C₅ to C₁₀ (5-alkyl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy, or C₁₀ to C₁₄ (5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy;

25 R⁶ and R⁷ are each independently selected from H, C₁-C₁₀ alkyl, hydroxy, C₁-C₁₀ alkoxy, nitro, C₁-C₁₀ alkylcarbonyl, -N(R¹²)R¹³, cyano, or halo;

30 R¹² and R¹³ are each independently selected from H, C₁-C₁₀ alkyl, C₁-C₁₀ alkoxy carbonyl, C₁-C₁₀ alkylcarbonyl, C₁-C₁₀ alkylsulfonyl, aryl(C₁-C₁₀ alkyl)sulfonyl, arylsulfonyl, heteroaryl carbonyl, heteroarylalkylcarbonyl or aryl, wherein said aryls are optionally substituted with 0-3 substituents selected from the group

311

consisting of: C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, CF₃, and NO₂;

5 R¹⁵ is selected from H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, aryl, heteroaryl or C₁-C₁₀ alkoxy carbonyl, CO₂R⁵ or -C(=O)N(R⁵)R^{5a};

10 R¹⁶ is selected from:
-C(=O)-O-R^{18a},
-C(=O)-R^{18b},
-C(=O)N(R^{18b})₂,
-SO₂-R^{18a}, or
-SO₂-N(R^{18b})₂;

15 R¹⁷ is selected from: H or C₁-C₄ alkyl

20 R^{18a} is selected from:
C₁-C₈ alkyl substituted with 0-2 R¹⁹,
C₂-C₈ alkenyl substituted with 0-2 R¹⁹,
C₂-C₈ alkynyl substituted with 0-2 R¹⁹,
C₃-C₈ cycloalkyl substituted with 0-2 R¹⁹,
aryl substituted with 0-4 R¹⁹,
aryl(C₁-C₆ alkyl) substituted with 0-4 R¹⁹,
25 a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, triazolyl, imidazolyl, benzofuranyl, indolyl, indolinyl, quinolinyl, isoquinolinyl, isoxazolinyl, benzimidazolyl, piperidinyl, tetrahydrofuran, pyran, pyrimidinyl, 3H-indolyl, carbazolyl, 30 pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-4 R¹⁹;

312

5 C_1 - C_6 alkyl substituted with a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolinyl, benzofuranyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuran, pyran, pyridinyl, 3H-indolyl, indolyl, carbazole, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-4 R^{19} ;

10 R^{18b} is selected from R^{18a} or H;

15 R^{19} is selected from H, halogen, CF_3 , CN, NO_2 , $NR^{12}R^{13}$, C_1 - C_8 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, C_3 - C_{11} cycloalkyl, C_4 - C_{11} cycloalkylalkyl, 16 aryl, heteroaryl, aryl(C_1 - C_6 alkyl), or C_1 - C_4 alkoxy carbonyl;

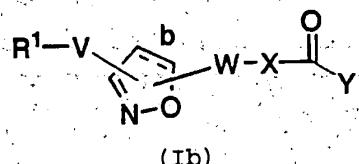
20 n is 0-4;

25 q is 1-7;

r is 0-3;

provided that n , q , and r are chosen such that the number of in-chain atoms between R^1 and Y is in the range of 8-17.

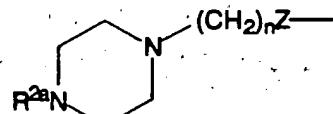
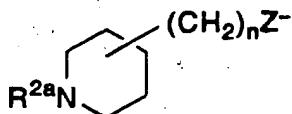
30 12. A compound of Claim 11 of Formula Ib.



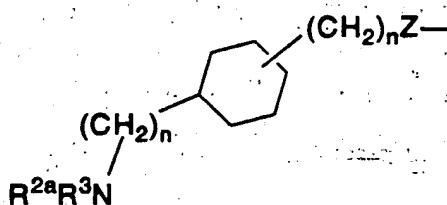
wherein:

R¹ is selected from: R²(R³)N-, R²NH(R²N=)C-,
 R²NH(R²N=)CNH-, R²R³N(CH₂)_pZ-,
 R²NH(R²N=)CNH(CH₂)_pZ- or

5



or



n is 0-1;

10 p' is 4-6;

p" is 2-4;

Z is selected from a bond or O;

15 V is a single bond, -(phenyl)- or -(pyridyl)-;

W is selected from:

- (C(R⁴)₂) - C(=O) - N(R^{5a}) -;
- C(=O) - N(R^{5a}) - CH₂ -;

20

X is selected from:

- CH₂ - CHN(R¹⁶)R¹⁷ - , or
- CH₂ - CHNR⁵R^{5a} -;

25 Y is selected from:

hydroxy;

C₁ to C₁₀ alkoxy;

methylcarbonyloxymethoxy-;

ethylcarbonyloxymethoxy-;

314

t-butylcarbonyloxymethoxy-;
cyclohexylcarbonyloxymethoxy-;
1-(methylcarbonyloxy)ethoxy-;
1-(ethylcarbonyloxy)ethoxy-;
5 1-(t-butylcarbonyloxy)ethoxy-;
1-(cyclohexylcarbonyloxy)ethoxy-;
i-propyloxycarbonyloxymethoxy-;
t-butyloxycarbonyloxymethoxy-;
1-(i-propyloxycarbonyloxy)ethoxy-;
10 1-(cyclohexyloxycarbonyloxy)ethoxy-;
1-(t-butyloxycarbonyloxy)ethoxy-;
dimethylaminoethoxy-;
diethylaminoethoxy-;
(5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;
15 (5-(t-butyl)-1,3-dioxacyclopenten-2-on-4-
yl)methoxy-;
(1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methoxy-;
1-(2-(2-methoxypropyl)carbonyloxy)ethoxy-;

20 R^{16} is selected from:

-C(=O)-O-R^{18a},
-C(=O)-R^{18b},
-S(=O)₂-R^{18a} or
-SO₂-N(R^{18b})₂;

25

R^{17} is selected from H or C₁-C₅ alkyl;

R^{18a} is selected from:

C₁-C₈ alkyl substituted with 0-2 R¹⁹,
30 C₂-C₈ alkenyl substituted with 0-2 R¹⁹,
C₂-C₈ alkynyl substituted with 0-2 R¹⁹,
C₃-C₈ cycloalkyl substituted with 0-2 R¹⁹,
aryl substituted with 0-4 R¹⁹,
aryl(C₁-C₆ alkyl)- substituted with 0-4 R¹⁹,

35

a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, triazolyl, imidazolyl, benzofuranyl, indolyl,

5 indolinyl, quinolinyl, isoquinolinyl, isoxazolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranlyl, pyrimidinyl, 3H-indolyl, carbazolyl, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-4 R¹⁹;

10

C₁-C₆ alkyl substituted with a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolinyl, benzofuranyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranlyl, pyridinyl, 3H-indolyl, indolyl, carbazole, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-4 R¹⁹.

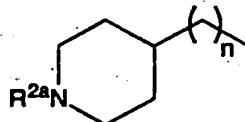
15

13. A compound of Claim 11 wherein:

R¹ is R²N(R²N=)C- or R²HN(R²N=)CNH- and V is phenylene or pyridylene, or

20

R¹ is



and V is a single bond;

n is 1 or 2;

30

R^{18a} is selected from:

C₁-C₄ alkyl substituted with 0-2 R¹⁹,

C₂-C₄ alkenyl substituted with 0-2 R¹⁹,

316

C₂-C₄ alkynyl substituted with 0-2 R¹⁹,

C₃-C₇ cycloalkyl substituted with 0-2 R¹⁹,

aryl substituted with 0-4 R¹⁹,

aryl(C₁-C₄ alkyl)- substituted with 0-4 R¹⁹,

5

a heterocyclic ring system selected from pyridinyl,

furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl,

triazolyl, imidazolyl, benzofuranyl, indolyl,

indolinyl, quinolinyl, isoquinolinyl, isoxazolinyl,

10

benzimidazolyl, piperidinyl, tetrahydrofuranyl,

pyranyl, pyrimidinyl, 3H-indolyl, carbazolyl,

pyrrolidinyl, piperidinyl, indolinyl, isoxazolinyl

or morpholinyl, said heterocyclic ring being

substituted with 0-4 R¹⁹;

15

C₁-C₄ alkyl substituted with a heterocyclic ring

system selected from pyridinyl, furanyl, thiazolyl,

thienyl, pyrrolyl, pyrazolyl, imidazolyl,

isoxazolinyl, benzofuranyl, indolyl, indolenyl,

20

quinolinyl, isoquinolinyl, benzimidazolyl,

piperidinyl, tetrahydrofuran, pyranyl, pyridinyl,

3H-indolyl, indolyl, carbazole, pyrrolidinyl,

piperidinyl, indolinyl, isoxazolinyl or

morpholinyl, said heterocyclic ring being

25

substituted with 0-4 R¹⁹.

14. A compound of Claim 6, or pharmaceutically

acceptable salt forms thereof, selected from:

30 N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-

acetyl]-N²- (phenylsulfonyl)-2,3-(S)-

diaminopropanoic acid;

N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-

acetyl]-N²- (4-methyl-phenyl-sulfonyl)-2,3-(S)-

35

diaminopropanoic acid;

N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-acetyl]-N₂-(butanesulfonyl)-2,3-(S)-diaminopropanoic acid;

5 N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-acetyl]-N₂-(propanesulfonyl)-2,3-(S)-diaminopropanoic acid;

N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-acetyl]-N₂-(ethanesulfonyl)-2,3-(S)-diaminopropanoic acid;

10 N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-acetyl]-N₂-(methyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-acetyl]-N₂-(ethyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

15 N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-acetyl]-N₂-(1-propyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-acetyl]-N₂-(2-propyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

20 N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-acetyl]-N₂-(n-butyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-acetyl]-N₂-(n-butyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

25 N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R)-yl}-acetyl]-N₂-(n-butyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(S)-yl}-acetyl]-N₂-(n-butyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

30 N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R)-yl}-acetyl]-N₂-(n-butyloxycarbonyl)-2,3-(R)-diaminopropanoic acid;

N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(S)-yl]-

5 acetyl]-N2-(n-butyloxycarbonyl)-2,3-(R)-

diaminopropanoic acid;

N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl]-

10 acetyl]-N2-(2-butyloxycarbonyl)-2,3-(S)-

diaminopropanoic acid;

N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl]-

15 acetyl]-N2-(1-(2-methyl)-propyloxycarbonyl)-2,3-

(S)-diaminopropanoic acid;

N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl]-

15 acetyl]-N2-(2-(2-methyl)-propyloxycarbonyl)-2,3-

(S)-diaminopropanoic acid;

N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl]-

15 acetyl]-N2-(benzyloxycarbonyl)-2,3-(S)-

diaminopropanoic acid;

N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(R)-yl]-

15 acetyl]-N2-(benzyloxycarbonyl)-2,3-(S)-

diaminopropanoic acid;

N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(S)-yl]-

20 acetyl]-N2-(benzyloxycarbonyl)-2,3-(S)-

diaminopropanoic acid;

N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl]-

25 acetyl]-N2-(4-methylbenzyloxycarbonyl)-2,3-(S)-

diaminopropanoic acid;

N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl]-

25 acetyl]-N2-(4-methoxybenzyloxycarbonyl)-2,3-(S)-

diaminopropanoic acid;

N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl]-

30 acetyl]-N2-(4-chlorobenzyloxycarbonyl)-2,3-(S)-

diaminopropanoic acid;

N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl]-

35 acetyl]-N2-(4-bromobenzyloxycarbonyl)-2,3-(S)-

diaminopropanoic acid;

N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-acetyl]-N2-(4-fluorobenzylloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

5 N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-acetyl]-N2-(4-phenoxybenzylloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

10 N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-acetyl]-N2-(2-(methyloxethyl)-oxycarbonyl)-2,3-(S)-diaminopropanoic acid;

15 N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-acetyl]-N2-(2-pyridinylcarbonyl)-2,3-(S)-diaminopropanoic acid;

20 N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-acetyl]-N2-(3-pyridinylcarbonyl)-2,3-(S)-diaminopropanoic acid;

25 N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-acetyl]-N2-(2-(2-pyridinyl)-acetyl)-2,3-(S)-diaminopropanoic acid;

30 N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-acetyl]-N2-(2-(3-pyridinyl)-acetyl)-2,3-(S)-diaminopropanoic acid;

N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-acetyl]-N2-(2-pyridyl-methyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-acetyl]-N2-(3-pyridyl-methyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

320

N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl]-acetyl]-N₂-(4-pyridyl-methyloxycarbonyl)-2,3-(S)-diaminopropanoic acid.

5 N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl]-acetyl]-N₂-(4-butyloxypyhenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl]-acetyl]-N₂-(2-thienylsulfonyl)-2,3-(S)-diaminopropanoic acid;

10 N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl]-acetyl]-N₂-(3-methylphenylsulfonyl)-2,3-(R,S)-diaminopropanoic acid;

N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl]-acetyl]-N₂-(3-methylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

15 N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl]-acetyl]-N₂-(3-methylphenylsulfonyl)-2,3-(R)-diaminopropanoic acid;

N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(R)-yl]-acetyl]-N₂-(3-methylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

20 N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(S)-yl]-acetyl]-N₂-(3-methylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(S)-yl]-acetyl]-N₂-(3-methylphenylsulfonyl)-2,3-(R)-diaminopropanoic acid;

25 N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(S)-yl]-acetyl]-N₂-(3-methylphenylsulfonyl)-2,3-(R)-diaminopropanoic acid;

N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(R)-yl]-acetyl]-N₂-(3-methylphenylsulfonyl)-2,3-(R)-diaminopropanoic acid;

30 N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl]-acetyl]-N₂-(4-iodophenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

321

N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-acetyl]-N2-(3-trifluoromethylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

5 N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-acetyl]-N2-(3-chlorophenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

10 N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-acetyl]-N2-(3-2-methoxycarbonylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

15 N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-acetyl]-N2-(2-chlorophenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

20 N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-acetyl]-N2-(2-trifluoromethylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

25 N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-acetyl]-N2-(2-fluorophenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

30 N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-acetyl]-N2-(4-fluorophenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-acetyl]-N2-(4-methoxyphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

35 N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-acetyl]-N2-(2,3,5,6-tetramethylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

322

5 N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl]-acetyl]-N2-(4-cyanophenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

10 N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl]-acetyl]-N2-(4-chlorophenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

15 N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl]-acetyl]-N2-(4-propylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

20 N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl]-acetyl]-N2-(2-phenylethylsulfonyl)-2,3-(S)-diaminopropanoic acid;

25 N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl]-acetyl]-N2-(4-isopropylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

30 N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl]-acetyl]-N2-(3-phenylpropylsulfonyl)-2,3-(S)-diaminopropanoic acid;

35 N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl]-acetyl]-N2-(3-pyridylsulfonyl)-2,3-(S)-diaminopropanoic acid;

40 N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl]-acetyl]-N2-(phenylaminosulfonyl)-2,3-(S)-diaminopropanoic acid;

45 N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl]-acetyl]-N2-(benzylaminosulfonyl)-2,3-(S)-diaminopropanoic acid;

50 N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl]-acetyl]-N2-(dimethylaminosulfonyl)-2,3-(S)-diaminopropanoic acid;

55 N³-[2-[3-(2-fluoro-4-formamidinophenyl)-isoxazolin-5(R,S)-yl]-acetyl]-N2-(3-methylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid.

N³-[2-[3-(2-formamidino-5-pyridinyl)-isoxazolin-5(R,S)-yl]-acetyl]-N2-(n-butyloxycarbonyl)-2,3-(S)-diaminopropanoic acid,

5 N³-[2-[3-(2-formamidino-5-pyridinyl)-isoxazolin-5(R,S)-yl]-acetyl]-N2-(3-methylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid,

10 N³-[2-[3-(3-formamidino-6-pyridinyl)-isoxazolin-5(R,S)-yl]-acetyl]-N2-(n-butyloxycarbonyl)-2,3-(S)-diaminopropanoic acid,

15 N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl]-acetyl]-N2-(phenylaminocarbonyl)-2,3-(S)-diaminopropanoic acid;

20 N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl]-acetyl]-N2-(4-fluorophenylaminocarbonyl)-2,3-(S)-diaminopropanoic acid;

25 N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl]-acetyl]-N2-(1-naphthylaminocarbonyl)-2,3-(S)-diaminopropanoic acid;

30 N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl]-acetyl]-N2-(3-methyl-2-benzothienylsulfonyl)-2,3-(S)-diaminopropanoic acid,

N³-[2-[3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl]-acetyl]-N2-(isobutyloxycarbonyl)-2,3-(S)-diaminopropanoic acid,

N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R)-yl}-acetyl]-N2-(isobutyloxycarbonyl)-2,3-(S)-diaminopropanoic acid,

5 N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(S)-yl}-acetyl]-N2-(isobutyloxycarbonyl)-2,3-(S)-diaminopropanoic acid,

10 N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R,S)-yl}-acetyl]-N2-(2-cyclopropylethoxycarbonyl)-2,3-(S)-diaminopropanoic acid,

15 N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(R)-yl}-acetyl]-N2-(2-cyclopropylethoxycarbonyl)-2,3-(S)-diaminopropanoic acid, and

N³-[2-{3-(4-formamidinophenyl)-isoxazolin-5(S)-yl}-acetyl]-N2-(2-cyclopropylethoxycarbonyl)-2,3-(S)-

20 15 diaminopropanoic acid.

N³-[2-{3-(4-guanidinophenyl)-isoxazolin-5(R,S)-yl}-acetyl]-N2-(n-butyloxycarbonyl)-2,3-(S)-diaminopropanoic acid.

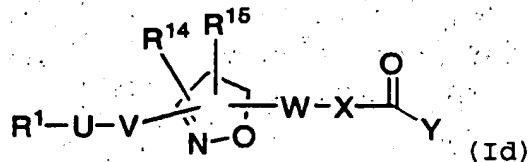
25 N³-[2-{3-(4-guanidinophenyl)-isoxazolin-5(R)-yl}-acetyl]-N2-(n-butyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

15. A prodrug ester of a compound of Claim 14,
30 said ester being selected from the group consisting of:
methyl;
ethyl;
isopropyl;
methylcarbonyloxymethyl-;
35 ethylcarbonyloxymethyl-;

t-butylcarbonyloxymethyl-;
 cyclohexylcarbonyloxymethyl-;
 1-(methylcarbonyloxy)ethyl-;
 1-(ethylcarbonyloxy)ethyl-;
 5 1-(t-butylcarbonyloxy)ethyl-;
 1-(cyclohexylcarbonyloxy)ethyl-;
 i-propyloxycarbonyloxymethyl-;
 cyclohexylcarbonyloxymethyl-;
 t-butyloxycarbonyloxymethyl-;
 10 1-(i-propyloxycarbonyloxy)ethyl-;
 1-(cyclohexyloxycarbonyloxy)ethyl-;
 1-(t-butyloxycarbonyloxy)ethyl-;
 dimethylaminoethyl-;
 diethylaminoethyl-;
 15 (5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methyl-;
 (5-(t-butyl)-1,3-dioxacyclopenten-2-on-
 4-yl)methyl-;
 (1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methyl-;
 1-(2-(2-methoxypropyl)carbonyloxy)ethyl-.

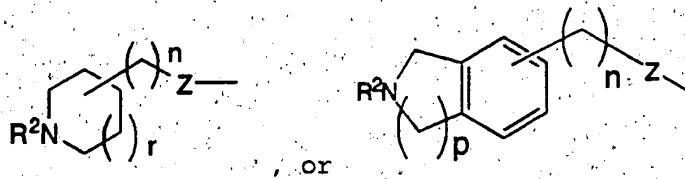
20

16. A compound of Formula Id:



25 or a pharmaceutically acceptable salt form thereof
 wherein:

R¹ is selected from is selected from R²(R³)N-,
 R²(R³)N(R²N=)C-, R²(R³)N(R²N=)CN(R²)-,
 30 R²(R³)N(CH₂)_qZ-, R²(R³)N(R²N=)C(CH₂)_qZ-,
 R²(R³)N(R²N=)CN(R²)(CH₂)_qZ-, piperazinyl-(CH₂)_qZ-,
 or



Z is selected from a bond, O, S, S(=O), or S(=O)2;

5 R² and R³ are independently selected from: H, C₁-C₁₀ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, C₆-C₁₀ aryl, C₇-C₁₁ arylalkyl, C₂-C₇ alkylcarbonyl, C₇-C₁₁ arylcarbonyl, C₂-C₁₀ alkoxy carbonyl, C₄-C₁₁ cycloalkoxycarbonyl, C₇-C₁₁ bicycloalkoxycarbonyl, C₇-C₁₁ aryloxycarbonyl, or 10 aryl(C₁-C₁₀ alkoxy)carbonyl, C₁-C₆ alkylcarbonyloxy(C₁-C₄ alkoxy)carbonyl, C₆-C₁₀ arylcarbonyloxy(C₁-C₄ alkoxy)carbonyl, C₄-C₁₁ cycloalkylcarbonyloxy(C₁-C₄ alkoxy)carbonyl;

15 U is selected from:

a single bond,
C₁-C₇ alkylene,
C₂-C₇ alkenylene,
20 C₂-C₇ alkynylene,
arylene substituted with 0-3 R^{6a}, or
pyridylene substituted with 0-3 R^{6a};

V is selected from:

25 a single bond;
C₁-C₇ alkylene substituted with 0-6 R⁶ or R⁷;
C₂-C₇ alkenylene substituted with 0-4 R⁶ or R⁷;
C₂-C₇ alkynylene substituted with 0-4 R⁶ or R⁷;
phenylene substituted with 0-4 R⁶ or R⁷;
30 pyridylene substituted with 0-3 R⁶ or R⁷;
pyridazinylene substituted with 0-3 R⁶ or R⁷;

327

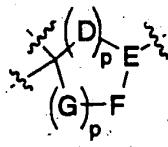
X is selected from:
a single bond;
-(CH₂)_nC(=O)N(R¹²)-;

5 C₁-C₇ alkylene substituted with 0-6 R⁴, R⁸ or R¹⁵;
C₂-C₇ alkenylene substituted with 0-4 R⁴, R⁸ or R¹⁵;
C₂-C₇ alkynylene substituted with 0-4 R⁴, R⁸ or R¹⁵;

Y is selected from:
hydroxy,
10 C₁ to C₁₀ alkyloxy,
C₃ to C₁₁ cycloalkyloxy,
C₆ to C₁₀ aryloxy,
C₇ to C₁₁ aralkyloxy,
C₃ to C₁₀ alkylcarbonyloxyalkyloxy,
15 C₃ to C₁₀ alkoxy carbonyloxyalkyloxy,
C₂ to C₁₀ alkoxy carbonylalkyloxy,
C₅ to C₁₀ cycloalkylcarbonyloxyalkyloxy,
C₅ to C₁₀ cycloalkoxycarbonyloxyalkyloxy,
C₅ to C₁₀ cycloalkoxycarbonylalkyloxy,
20 C₇ to C₁₁ aryloxycarbonylalkyloxy,
C₈ to C₁₂ aryloxycarbonyloxyalkyloxy,
C₈ to C₁₂ arylcarbonyloxyalkyloxy,
C₅ to C₁₀ alkoxyalkylcarbonyloxyalkyloxy,
C₅ to C₁₀ (5-alkyl-1,3-dioxa-cyclopenten-2-one-
25 yl)methyloxy,
C₁₀ to C₁₄ (5-aryl-1,3-dioxa-cyclopenten-2-one-
yl)methyloxy;
(R²)₂N-(C₁-C₁₀ alkoxy)-;

30 R¹⁴ and W are attached to the same carbon and taken together to form a spiro-fused, 5-7 membered ring structure of the formula:

328



D, E, F and G are each independently selected from:

$C(R^{6a})_2$;

5 carbonyl;

a heteroatom moiety selected from N, N(R^{12}), O,

provided that no more than 2 of D, E, F and G

are N, N(R^{12}), O, S, or C(=O);

alternatively, the bond between D and E, E and F, or F

10 and G in such spiro-fused ring may be a

carbon-nitrogen double bond or a carbon-carbon

double bond;

R^4 is selected from H, C₁-C₁₀ alkyl, hydroxy, C₁-C₁₀ 15 alkoxy, nitro, C₁-C₁₀ alkylcarbonyl, or -N(R^{12})R¹³;

R^6 and R^7 are each independently selected from H, C₁-C₁₀ 20 alkyl, hydroxy, C₁-C₁₀ alkoxy, nitro, C₁-C₁₀ alkylcarbonyl, -N(R^{12})R¹³, cyano, halo, CF₃, CHO,

CO₂R^{5a}, C(=O)R^{5a}, CONHR^{5a}, CON(R^{12})₂, OC(=O)R^{5a},

OC(=O)OR^{5a}, OR^{5a}, OC(=O)N(R^{12})₂, OCH₂CO₂R^{5a},

CO₂CH₂CO₂R^{5a}, N(R^{12})₂, NO₂, NR¹²C(=O)R^{5a},

NR¹²C(=O)OR^{5a}, NR¹²C(=O)N(R^{12})₂, NR¹²SO₂N(R^{12})₂,

NR¹²SO₂R^{5a}, S(O)pR^{5a}, SO₂N(R^{12})₂, C₂ to C₆ alkenyl,

25 C₃ to C₁₁ cycloalkyl, C₄ to C₁₁ cycloalkylmethyl;

C₆ to C₁₀ aryl optionally substituted with 1-3 groups selected from halogen, C₁-C₆ alkoxy, C₁-C₆ alkyl, CF₃, S(O)_mMe, or -NMe₂;

30

C_7 to C_{11} arylalkyl, said aryl being optionally substituted with 1-3 groups selected from halogen, C_1 - C_6 alkoxy, C_1 - C_6 alkyl, CF_3 , $S(O)_mMe$, or $-NMe_2$;

5 methylenedioxy when R^6 is a substituent on aryl;

R^{6a} is selected from C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halo, CF_3 , NO_2 , or $NR^{12}R^{13}$;

10 R^8 is selected from:

H;

R^6 ;

C_1 - C_{10} alkyl, substituted with 0-8 R^6 ;

C_2 - C_{10} alkenyl, substituted with 0-6 R^6 ;

15 C_2 - C_{10} alkynyl, substituted with 0-6 R^6 ;

C_3 - C_8 cycloalkyl, substituted with 0-6 R^6 ;

C_5 - C_6 cycloalkenyl, substituted with 0-5 R^6 ;

aryl, substituted with 0-5 R^6 ;

5-6 membered heterocyclic ring containing 1-2 N, O,

20 or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-5 R^6 ;

25 R^{12} and R^{13} are independently H, C_1 - C_{10} alkyl, C_1 - C_{10} alkoxy carbonyl, C_1 - C_{10} alkyl carbonyl, C_1 - C_{10} alkylsulfonyl, aryl(C_1 - C_{10} alkyl)sulfonyl, arylsulfonyl, aryl, C_2 - C_6 alkenyl, C_3 - C_{11} cycloalkyl, C_4 - C_{11} cycloalkylalkyl, C_7 - C_{11} arylalkyl, 30 C_2 - C_7 alkyl carbonyl, C_7 - C_{11} aryl carbonyl, C_2 - C_{10} alkoxy carbonyl, C_4 - C_{11} cycloalkoxy carbonyl, C_7 - C_{11} bicycloalkoxy carbonyl, C_7 - C_{11} aryloxycarbonyl, heteroaryl carbonyl, heteroarylalkyl carbonyl or aryl(C_1 - C_{10} alkoxy) carbonyl, wherein said aryls or heteroaryl are optionally substituted with 0-3

substituents selected from the group consisting of:
C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, CF₃, and NO₂;

R⁵ and R^{5a} are selected independently from H, C₁ to C₈
5 alkyl, C₂ to C₆ alkenyl, C₃ to C₁₁ cycloalkyl, C₄ to
C₁₁ cycloalkylmethyl, C₆ to C₁₀ aryl, C₇ to C₁₁
arylalkyl, or C₁-C₁₀ alkyl substituted with 0-8 R⁴;

R¹⁵ is selected from:

10 H;
R⁶;
C₁-C₁₀ alkyl, substituted with 0-8 R⁶;
C₂-C₁₀ alkenyl, substituted with 0-6 R⁶;

C₁-C₁₀ alkoxy, substituted with 0-6 R⁶;

15 aryl, substituted with 0-5 R⁶;
5-6 membered heterocyclic ring containing 1-2 N, O,
or S heteroatoms, wherein said heterocyclic
ring may be saturated, partially saturated, or
fully unsaturated, said heterocyclic ring
20 being substituted with 0-5 R⁶;
C₁-C₁₀ alkoxy carbonyl substituted with 0-8 R⁶;
CO₂R⁵; or
-C(=O)N(R¹²)R¹³;

25 n is 0-4;

p is 1-3;

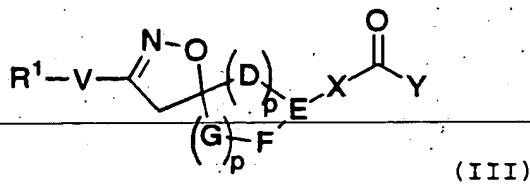
q is 1-7;

r is 0-3;

provided that n, p, q and r are chosen such that the

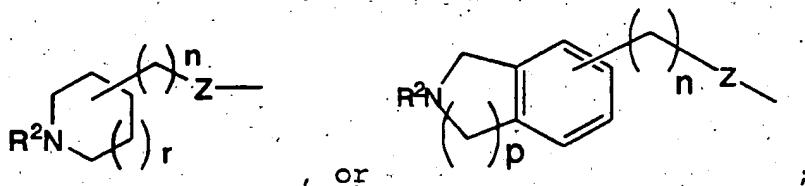
30 number of atoms between R¹ and Y is in the range of
8-17.

17. A compound of Claim 16 of Formula III:



wherein:

5 R¹ is selected from R²HN-, H₂N(R²N=)C-, H₂N(R²N=)CNH-, R²HN(CH₂)_qO-, H₂N(R²N=)CNH(CH₂)_qO-, piperazinyl-(CH₂)_qO-,



10 R² is selected from H, aryl(C₁-C₁₀ alkoxy)carbonyl, or C₁-C₁₀ alkoxy carbonyl;

R⁴ is selected from H; C₁-C₁₀ alkyl, hydroxy, C₁-C₁₀ alkoxy, nitro, C₁-C₁₀ alkylcarbonyl, or -N(R¹²)R¹³;

15 V is selected from:
a single bond;
C₁-C₇ alkylene substituted with 0-6 R⁶ or R⁷;
C₂-C₇ alkenylene substituted with 0-4 R⁶ or R⁷;
20 C₂-C₇ alkynylene substituted with 0-4 R⁶ or R⁷;
phenylene substituted with 0-3 R⁶ or R⁷;
pyridylene substituted with 0-3 R⁶ or R⁷;
pyridazinylene substituted with 0-3 R⁶ or R⁷;

25 X is selected from -(CH₂)_nC(=O)N(R¹²)-, C₁-C₇ alkylene substituted with 0-1 R⁴, C₂-C₇ alkenylene, or C₂-C₇ alkynylene;

Y is selected from:

hydroxy,
C₁ to C₁₀ alkyloxy,
C₃ to C₁₁ cycloalkyloxy,
C₆ to C₁₀ aryloxy,
5 C₇ to C₁₁ aralkyloxy,
C₃ to C₁₀ alkylcarbonyloxyalkyloxy,
C₃ to C₁₀ alkoxy carbonyloxyalkyloxy,
C₂ to C₁₀ alkoxy carbonylalkyloxy,
C₅ to C₁₀ cycloalkylcarbonyloxyalkyloxy,
10 C₅ to C₁₀ cycloalkoxycarbonyloxyalkyloxy,
C₅ to C₁₀ cycloalkoxycarbonylalkyloxy,
C₇ to C₁₁ aryloxycarbonylalkyloxy,
C₈ to C₁₂ aryloxycarbonyloxyalkyloxy,
C₈ to C₁₂ arylcarbonyloxyalkyloxy,
15 C₅ to C₁₀ alkoxyalkylcarbonyloxyalkyloxy,
C₅ to C₁₀ (5-alkyl-1,3-dioxa-cyclopenten-2-one-
yl)methyloxy, or
C₁₀ to C₁₄ (5-aryl-1,3-dioxa-cyclopenten-2-one-
yl)methyloxy;
20 Z is selected from O or CH₂;

D, E, F and G are each independently selected from:
CH₂;
25 carbonyl;
a heteroatom moiety selected from N, NH, O, provided
that no more than 2 of D, E, F and G are N, NH,
O or S;
alternatively, the bond between D and E, E and F, or F
30 and G in such spiro-fused ring may be a
carbon-nitrogen double bond or a carbon-carbon
double bond;

R⁶ and R⁷ are each independently selected from H, C₁-C₁₀
35 alkyl, hydroxy, C₁-C₁₀ alkoxy, nitro, C₁-C₁₀
alkylcarbonyl, -N(R¹²)R¹³, cyano, or halo;

R^{12} and R^{13} are each independently selected from H, C_1-C_{10} alkyl, C_1-C_{10} alkoxy carbonyl, C_1-C_{10} alkyl carbonyl, C_1-C_{10} alkylsulfonyl, aryl(C_1-C_{10} alkyl)sulfonyl, arylsulfonyl, heteroaryl carbonyl, heteroaryl alkyl carbonyl or aryl;

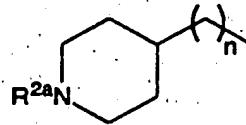
5 n is 0-4;
 p is 1-3;
 10 q is 1-7;
 r is 0-3;

provided that n, p, q and r are chosen such that the number of atoms between R^1 and Y is in the range of 8-17.

15

18. A compound of Claim 17 wherein:

20 R^1 is $R^2NHC(=NR^2)-$ and V is phenyl or pyridyl or R^1 is



and V is a single bond;

25 n is 1 or 2;

25 X is C_1-C_4 alkylene substituted with 0-1 R^4 ;

30 Y is selected from:
 hydroxy;
 C_1 to C_{10} alkoxy;
 methylcarbonyloxymethoxy-;
 ethylcarbonyloxymethoxy-;
 t -butylcarbonyloxymethoxy-;
 cyclohexylcarbonyloxymethoxy-;

1-(methylcarbonyloxy)ethoxy-;
1-(ethylcarbonyloxy)ethoxy-;
1-(t-butylcarbonyloxy)ethoxy-;
1-(cyclohexylcarbonyloxy)ethoxy-;
5 i-propyloxycarbonyloxymethoxy-;
t-butyloxycarbonyloxymethoxy-;
1-(i-propyloxycarbonyloxy)ethoxy-;
1-(cyclohexyloxycarbonyloxy)ethoxy-;
1-(t-butyloxycarbonyloxy)ethoxy-;
10 dimethylaminoethoxy-;
diethylaminoethoxy-;
(5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;
(5-(t-butyl)-1,3-dioxacyclopenten-2-on-4-
y1)methoxy-;
15 (1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methoxy-;
1-(2-(2-methoxypropyl)carbonyloxy)ethoxy-;

R¹² and R¹³ are each independently selected from H, C₁-C₆ alkyl, C₁-C₄ alkoxy carbonyl, C₁-C₄ alkyl carbonyl, C₁-C₄ alkylsulfonyl, aryl(C₁-C₄ alkyl)sulfonyl, arylsulfonyl, heteroaryl carbonyl, heteroaryl alkyl carbonyl or aryl; and

R¹³ is H.

25

19. A compound of Claim 16, or pharmaceutically acceptable salt forms thereof, selected from:

30 5(R,S)-3-(4-amidinophenyl)-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]non-2-ene-7,9-dione;
5(R,S)-3-(4-amidinophenyl)-8-(3-carboxypropyl)-1-oxa-2,8-diazaspiro[4.4]non-2-ene-7,9-dione;
5(R,S)-3-(4-amidinophenyl)-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]non-2-ene-5-one;

5 (*R,S*) -3- (4-amidinophenyl) -8- (3-carboxypropyl) -1-oxa-
2,8-diazaspiro[4.4]non-2-ene-5-one;

5 (*R,S*) -3- (4-amidinophenyl) -8- (2-carboxyethyl) -1-oxa-2-
azaspiro[4.4]nona-2,8-diene-5-one;

5 5 (*R,S*) -3- (4-amidinophenyl) -8- (3-carboxypropyl) -1-oxa-2-
azaspiro[4.4]nona-2,8-diene-5-one;

5 (*R,S*) -3- (4-amidinophenyl) -8- (2-carboxyethyl) -1-oxa-2,8-
diazaspiro[4.4]dec-2-ene-7,9-dione;

5 (*R,S*) -3- (4-amidinophenyl) -8- (3-carboxypropyl) -1-oxa-
2,8-diazaspiro[4.4]dec-2-ene-7,9-dione;

10 5 (*R,S*) -3- (4-amidinophenyl) -8- (2-carboxyethyl) -1-oxa-2,8-
diazaspiro[4.4]dec-2-ene-5-one;

5 (*R,S*) -3- (4-amidinophenyl) -8- (3-carboxypropyl) -1-oxa-
2,8-diazaspiro[4.4]dec-2-ene-5-one;

15 5 (*R,S*) -3- (4-amidinophenyl) -8- (2-carboxyethyl) -1-oxa-2-
azaspiro[4.4]deca-2,8-diene-5-one;

5 (*R,S*) -3- (4-amidinophenyl) -8- (3-carboxypropyl) -1-oxa-2-
azaspiro[4.4]deca-2,8-diene-5-one;

5 (*R,S*) -3- (4-amidinophenyl) -8- (2-carboxyethyl) -1-oxa-2,8-
20 diazaspiro[4.4]undec-2-ene-7,9-dione;

5 (*R,S*) -3- (4-amidinophenyl) -8- (3-carboxypropyl) -1-oxa-
2,8-diazaspiro[4.4]undec-2-ene-7,9-dione;

5 (*R,S*) -3- (4-amidinophenyl) -8- (2-carboxyethyl) -1-oxa-2,8-
25 diazaspiro[4.4]undec-2-ene-5-one;

5 (*R,S*) -3- (4-amidinophenyl) -8- (3-carboxypropyl) -1-oxa-
2,8-diazaspiro[4.4]undec-2-ene-5-one;

5 (*R,S*) -3- (4-amidinophenyl) -8- (2-carboxyethyl) -1-oxa-2-
azaspiro[4.4]undeca-2,8-diene-5-one;

5 (*R,S*) -3- (4-amidinophenyl) -8- (3-carboxypropyl) -1-oxa-
30 2,8-diazaspiro[4.4]undeca-2,8-diene-5-one;

5 (*R,S*) -3- [2-(piperidin-4-yl)ethyl] -8- (2-carboxyethyl) -1-
oxa-2,8-diazaspiro[4.4]non-2-ene-7,9-dione;

5 (*R,S*) -3- [2-(piperidin-4-yl)ethyl] -8- (3-carboxypropyl) -
1-oxa-2,8-diazaspiro[4.4]non-2-ene-7,9-dione;

35 5 (*R,S*) -3- [2-(piperidin-4-yl)ethyl] -8- (2-carboxyethyl) -1-
oxa-2,8-diazaspiro[4.4]non-2-ene-5-one;

5 (R,S) -3- [2- (piperidin-4-yl)ethyl]-8- (3-carboxypropyl)-
1-oxa-2,8-diazaspiro[4.4]non-2-ene-5-one;

5 (R,S) -3- [2- (piperidin-4-yl)ethyl]-8- (2-carboxyethyl)-1-
oxa-2-azaspiro[4.4]nona-2,8-diene-5-one;

5 (R,S) -3- [2- (piperidin-4-yl)ethyl]-8- (3-carboxypropyl)-
1-oxa-2-azaspiro[4.4]nona-2,8-diene-5-one;

5 (R,S) -3- [2- (piperidin-4-yl)ethyl]-8- (2-carboxyethyl)-1-
oxa-2,8-diazaspiro[4.4]dec-2-ene-7,9-dione;

5 (R,S) -3- [2- (piperidin-4-yl)ethyl]-8- (3-carboxypropyl)-
1-oxa-2,8-diazaspiro[4.4]dec-2-ene-5,7-dione;

5 (R,S) -3- [2- (piperidin-4-yl)ethyl]-8- (2-carboxyethyl)-1-
oxa-2,8-diazaspiro[4.4]dec-2-ene-5-one;

5 (R,S) -3- [2- (piperidin-4-yl)ethyl]-8- (3-carboxypropyl)-
1-oxa-2,8-diazaspiro[4.4]dec-2-ene-5-one;

15 5 (R,S) -3- [2- (piperidin-4-yl)ethyl]-8- (2-carboxyethyl)-1-
oxa-2-azaspiro[4.4]deca-2,8-diene-5-one;

5 (R,S) -3- [2- (piperidin-4-yl)ethyl]-8- (3-carboxypropyl)-
1-oxa-2-azaspiro[4.4]deca-2,8-diene-5-one;

5 (R,S) -3- [2- (piperidin-4-yl)ethyl]-8- (2-carboxyethyl)-1-
oxa-2,8-diazaspiro[4.4]undec-2-ene-7,9-dione;

5 (R,S) -3- [2- (piperidin-4-yl)ethyl]-8- (3-carboxypropyl)-
1-oxa-2,8-diazaspiro[4.4]undec-2-ene-7,9-dione;

5 (R,S) -3- [2- (piperidin-4-yl)ethyl]-8- (2-carboxyethyl)-1-
oxa-2,8-diazaspiro[4.4]undec-2-ene-5-one;

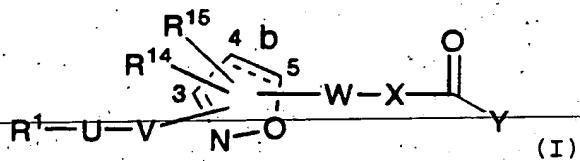
25 5 (R,S) -3- [2- (piperidin-4-yl)ethyl]-8- (3-carboxypropyl)-
1-oxa-2,8-diazaspiro[4.4]undec-2-ene-5-one;

5 (R,S) -3- [2- (piperidin-4-yl)ethyl]-8- (2-carboxyethyl)-1-
oxa-2-azaspiro[4.4]undeca-2,8-diene-5-one;

5 (R,S) -3- [2- (piperidin-4-yl)ethyl]-8- (3-carboxypropyl)-
1-oxa-2-azaspiro[4.4]undeca-2,8-diene-5-one;

30 5 (R,S) -3- (4-amidinophenyl)-8-
[2- (benzyloxycarbonylamino)-2-carboxyethyl]-1-oxa-
2,8-diazaspiro[4.5]dec-2-ene.

35 20. A compound of Formula I:



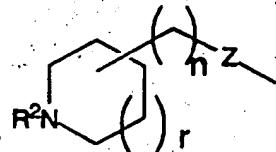
or pharmaceutically acceptable salt form thereof,
wherein:

5

R^1 is selected from:

$R^2(R^3)_qZ^-$, $R^2(R^3)N(R^2N=)C(CH_2)_qZ^-$,

$R^2(R^3)N(R^2N=)CN(R^2)(CH_2)_qZ^-$, piperazinyl- $(CH_2)_qZ^-$ or



10

Z is selected from O , S , $S(=O)$, $S(=O)_2$;

R^2 and R^3 are independently selected from: H , C_1-C_{10}
alkyl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11}
15 cycloalkylalkyl, C_6-C_{10} aryl, C_7-C_{11} arylalkyl, C_2-C_7
alkylcarbonyl, C_7-C_{11} arylcarbonyl, C_2-C_{10}
alkoxycarbonyl, C_4-C_{11} cycloalkoxycarbonyl, C_7-C_{11}
bicycloalkoxycarbonyl, C_7-C_{11} aryloxycarbonyl, or
20 aryl(C_1-C_{10} alkoxy)carbonyl, C_1-C_6
alkylcarbonyloxy(C_1-C_4 alkoxy)carbonyl, C_6-C_{10}
arylcarbonyloxy(C_1-C_4 alkoxy)carbonyl, C_4-C_{11}
cycloalkylcarbonyloxy(C_1-C_4 alkoxy)carbonyl;

U is optionally present and is selected from C_1-C_7
25 alkylene, C_2-C_7 alkenylene, C_2-C_7 alkynylene,
arylene, or pyridylene;

V is selected from:
a single bond;

338

C₁-C₇ alkylene substituted with 0-6 R⁶ or R⁷;
C₂-C₇ alkenylene substituted with 0-4 R⁶ or R⁷;
C₂-C₇ alkynylene substituted with 0-4 R⁶ or R⁷;
phenylene substituted with 0-4 R⁶ or R⁷;
5 pyridylene substituted with 0-3 R⁶ or R⁷;
pyridazinylene substituted with 0-3 R⁶ or R⁷;

W is -(aryl)-Z¹, wherein said aryl is substituted
with 0-6 R⁶ or R⁷;

10 Z¹ is selected from a single bond, -CH₂-, O or S;

X is selected from:
a single bond;

15 C₁-C₇ alkylene substituted with 0-6 R⁴, R⁸ or R¹⁵;
C₂-C₇ alkenylene substituted with 0-4 R⁴, R⁸ or R¹⁵;
C₂-C₇ alkynylene substituted with 0-4 R⁴, R⁸ or R¹⁵;

Y is selected from hydroxy, C₁ to C₁₀ alkyloxy, C₃ to
20 C₁₁ cycloalkyloxy, C₆ to C₁₀ aryloxy, C₇ to C₁₁
aralkyloxy, C₃ to C₁₀ alkylcarbonyloxyalkyloxy, C₃
to C₁₀ alkoxy carbonyloxyalkyloxy, C₂ to C₁₀
alkoxycarbonylalkyloxy, C₅ to C₁₀
cycloalkylcarbonyloxyalkyloxy, C₅ to C₁₀
25 cycloalkoxycarbonyloxyalkyloxy, C₅ to C₁₀
cycloalkoxycarbonylalkyloxy, C₇ to C₁₁
aryloxycarbonylalkyloxy, C₈ to C₁₂
aryloxycarbonyloxyalkyloxy, C₈ to C₁₂
arylcarbonyloxyalkyloxy, C₅ to C₁₀
30 alkoxyalkylcarbonyloxyalkyloxy, C₅ to C₁₀ (5-alkyl-
1,3-dioxa-cyclopenten-2-one-yl)methyloxy, C₁₀ to C₁₄
(5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy;
(R²)(R³)N-(C₁-C₁₀ alkoxy)-;

339

R⁴ is selected from H, C₁-C₁₀ alkyl, hydroxy, C₁-C₁₀ alkoxy, nitro, C₁-C₁₀ alkylcarbonyl, or -N(R¹²)R¹³;

R⁶ and R⁷ are each independently selected from H, C₁-C₁₀ alkyl, hydroxy, C₁-C₁₀ alkoxy, nitro, C₁-C₁₀ alkylcarbonyl, -N(R¹²)R¹³, cyano, halo, CF₃, CHO, CO₂R^{5a}, C(=O)R^{5a}, CONHR^{5a}, CON(R¹²)₂, OC(=O)R^{5a}, OC(=O)OR^{5a}, OR^{5a}, OC(=O)N(R¹²)₂, OCH₂CO₂R^{5a}, CO₂CH₂CO₂R^{5a}, N(R¹²)₂, NO₂, NR¹²C(=O)R^{5a}, NR¹²C(=O)OR^{5a}, NR¹²C(=O)N(R¹²)₂, NR¹²SO₂N(R¹²)₂, NR¹²SO₂R^{5a}, S(O)pR^{5a}, SO₂N(R¹²)₂, C₂ to C₆ alkenyl, C₃ to C₁₁ cycloalkyl, C₄ to C₁₁ cycloalkylmethyl; C₆ to C₁₀ aryl optionally substituted with halogen, alkoxy, alkyl, -CF₃, S(O)_mMe, or -NMe₂; or C₇ to C₁₁ arylalkyl said aryl being optionally substituted with halogen, alkoxy, alkyl, -CF₃, S(O)_mMe, or -NMe₂;

R⁸ is selected from: H; R⁶; C₁-C₁₀ alkyl, substituted with 0-8 R⁶; C₂-C₁₀ alkenyl, substituted with 0-6 R⁶; C₂-C₁₀ alkynyl, substituted with 0-6 R⁶; C₃-C₈ cycloalkyl, substituted with 0-6 R⁶; C₅-C₆ cycloalkenyl, substituted with 0-5 R⁶; aryl, substituted with 0-5 R⁶; 5-6 membered heterocyclic ring containing 1-2 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-5 R⁶;

R¹² and R¹³ are independently H, C₁-C₁₀ alkyl, C₁-C₁₀ alkoxy carbonyl, C₁-C₁₀ alkyl carbonyl, C₁-C₁₀ alkylsulfonyl, aryl(C₁-C₁₀ alkyl)sulfonyl, arylsulfonyl, aryl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, C₇-C₁₁ arylalkyl, C₂-C₇ alkyl carbonyl, C₇-C₁₁ aryl carbonyl, C₂-C₁₀ alkoxy carbonyl, C₄-C₁₁ cycloalkoxy carbonyl, C₇-C₁₁ bicycloalkoxy carbonyl, C₇-C₁₁ aryloxycarbonyl, heteroaryl carbonyl, heteroarylalkyl carbonyl or aryl(C₁-C₁₀ alkoxy) carbonyl;

R¹⁴ is selected from H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, aryl, heteroaryl or C₁-C₁₀ alkoxy carbonyl, CO₂R⁵ or -C(=O)N(R¹²)R¹³;

R⁵ and R^{5a} are selected independently from H, C₁ to C₈ alkyl, C₂ to C₆ alkenyl, C₃ to C₁₁ cycloalkyl, C₄ to C₁₁ cycloalkylmethyl, C₆ to C₁₀ aryl, C₇ to C₁₁ arylalkyl, or C₁-C₁₀ alkyl substituted with 0-8 R⁴;

R¹⁵ is selected from:
H;
R⁶;
C₁-C₁₀ alkyl, substituted with 0-8 R⁶;
C₂-C₁₀ alkenyl, substituted with 0-6 R⁶;
C₁-C₁₀ alkoxy, substituted with 0-6 R⁶;
aryl, substituted with 0-5 R⁶;
5-6 membered heterocyclic ring containing 1-2 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-5 R⁶;
C₁-C₁₀ alkoxy carbonyl substituted with 0-8 R⁶;
CO₂R⁵; or
-C(=O)N(R¹²)R¹³;

n is 0-4;

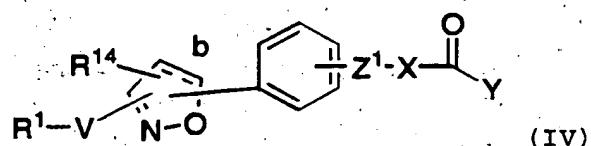
q is 2-7;

r is 0-3;

5 provided that n, q, and r are chosen such that the number of atoms between R¹ and Y is about 8-17.

21. A compound of Claim 20 of Formula IV:

10

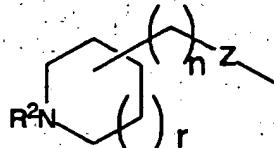


wherein:

R¹ is selected from R²HN(CH₂)_qO⁻,

R²HN(R²N=C)NH(CH₂)_qO⁻, piperazinyl-(CH₂)_qO⁻, or

15



Z is O;

20

R² is selected from H, aryl(C₁-C₁₀)alkoxycarbonyl,

C₁-C₁₀ alkoxycarbonyl;

V is selected from:

a single bond;

C₁-C₇ alkylene substituted with 0-6 R⁶ or R⁷;

C₂-C₇ alkenylene substituted with 0-4 R⁶ or R⁷;

25

C₂-C₇ alkynylene substituted with 0-4 R⁶ or R⁷;

phenylene substituted with 0-3 R⁶ or R⁷;

pyridylene substituted with 0-3 R⁶ or R⁷;

pyridazinylene substituted with 0-3 R⁶ or R⁷;

30

Z¹ is selected from a single bond, O or S;

X is selected from:
a single bond;
C₁-C₇ alkylene substituted with 0-4 R⁴, R⁸ or R¹⁵;
5 C₂-C₇ alkenylene substituted with 0-3 R⁴, R⁸ or R¹⁵;
C₂-C₇ alkynylene substituted with 0-3 R⁴, R⁸ or R¹⁵;

Y selected from hydroxy, C₁ to C₁₀ alkyloxy, C₃ to C₁₁ cycloalkyloxy, C₆ to C₁₀ aryloxy, C₇ to C₁₁ aralkyloxy, C₃ to C₁₀ alkylcarbonyloxyalkyloxy, C₃ to C₁₀ alkoxy carbonyloxyalkyloxy, C₂ to C₁₀ alkoxy carbonylalkyloxy, C₅ to C₁₀ cycloalkylcarbonyloxyalkyloxy, C₅ to C₁₀ cycloalkoxycarbonyloxyalkyloxy, C₅ to C₁₀ 15 cycloalkoxycarbonylalkyloxy, C₇ to C₁₁ aryloxycarbonylalkyloxy, C₈ to C₁₂ aryloxycarbonyloxyalkyloxy, C₈ to C₁₂ arylcarbonyloxyalkyloxy, C₅ to C₁₀ alkoxyalkylcarbonyloxyalkyloxy, C₅ to C₁₀ (5-alkyl-20 1,3-dioxa-cyclopenten-2-one-yl)methyloxy, or C₁₀ to C₁₄ (5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy;

R⁴ is selected from H, C₁-C₁₀ alkyl, hydroxy, C₁-C₁₀ 25 alkoxy, nitro, C₁-C₁₀ alkylcarbonyl, or -N(R¹²)R¹³;

R⁶ and R⁷ are selected from H, C₁-C₁₀ alkyl, hydroxy, C₁-C₁₀ alkoxy, nitro, C₁-C₁₀ alkylcarbonyl, -N(R¹²)R¹³, cyano, or halo;

30 R⁸ is selected from H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₃-C₈ cycloalkyl, C₅-C₆ cycloalkenyl, aryl, 5-6 membered heterocyclic ring containing 1-2 N, O, or S, where said heterocyclic ring may be saturated, 35 partially saturated, or fully unsaturated;

R¹² and R¹³ are independently selected from H, C₁-C₁₀ alkyl, C₁-C₁₀ alkoxycarbonyl, C₁-C₁₀ alkylcarbonyl, C₁-C₁₀ alkylsulfonyl, aryl(C₁-C₁₀ alkyl)sulfonyl, arylsulfonyl, heteroarylcarbonyl, heteroarylalkylcarbonyl or aryl;

5 R¹⁴ is selected from H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, aryl, heteroaryl or C₁-C₁₀ alkoxycarbonyl, CO₂R⁵ or -C(=O)N(R¹²)R¹³;

10 R⁵ is selected from H or C₁-C₁₀ alkyl substituted with 0-6 R⁴;

n is 0-4;

15 q is 2-7;

provided that n and q are chosen such that the number of atoms between R¹ and Y is in the range of 8-17.

22. A compound of Claim 21 wherein:

R¹ is R²HN(CH₂)_qO- or

V is C₁-C₃ alkylene;

25 Z¹ is a single bond or O;

X is C₁-C₃ alkylene substituted with 0-1 R⁴;

30 Y is selected from:

hydroxy;

C₁ to C₁₀ alkoxy;

methylcarbonyloxymethoxy-;

ethylcarbonyloxymethoxy-;

t-butylcarbonyloxymethoxy-;

344

cyclohexylcarbonyloxymethoxy-;
1-(methylcarbonyloxy)ethoxy-;
1-(ethylcarbonyloxy)ethoxy-;
1-(t-butylcarbonyloxy)ethoxy-;
5 1-(cyclohexylcarbonyloxy)ethoxy-;
i-propyloxycarbonyloxymethoxy-;
t-butyloxycarbonyloxymethoxy-;
1-(i-propyloxycarbonyloxy)ethoxy-;
1-(cyclohexyloxycarbonyloxy)ethoxy-;
10 1-(t-butyloxycarbonyloxy)ethoxy-;
dimethylaminoethoxy-;
diethylaminoethoxy-;
(5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;
(5-(t-butyl)-1,3-dioxacyclopenten-2-on-4-
15 yl)methoxy-;
(1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methoxy-;
1-(2-(2-methoxypropyl)carbonyloxy)ethoxy-;

R¹² and R¹³ are independently selected from H, C₁-C₆
20 alkyl, C₁-C₄ alkoxy carbonyl, C₁-C₄ alkyl carbonyl,
C₁-C₆ alkylsulfonyl, aryl(C₁-C₄ alkyl)sulfonyl,
arylsulfonyl, heteroaryl carbonyl,
heteroarylalkyl carbonyl or aryl;

25 R¹³ is H.

23. A compound of Claim 20, or a pharmaceutically acceptable salt form thereof, selected from:

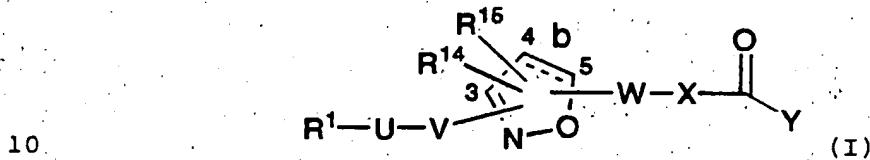
30 5(R,S)-4-[3-(piperidin-4-yl)oxymethyl]isoxazolin-5-yl]hydro-
drocinnamic acid;
5(R,S)-4-[3-(2-aminoethoxymethyl)isoxazolin-5-yl]hydro-
cinnamic acid;
5(R,S)-4-[3-(3-aminopropoxymethyl)isoxazolin-5-yl]hydro-
35 drocinnamic acid;

5 (R,S)-4-[3-(piperidin-4-yl)oxymethylisoxazolin-5-yl]phenoxyacetic acid;

5 (R,S)-4-[3-(2-aminoethoxymethyl)isoxazolin-5-yl]phenoxyacetic acid;

5 5 (R,S)-4-[3-(3-aminopropylloxymethyl)isoxazolin-5-yl]phenoxyacetic acid.

24. A compound of Formula I:

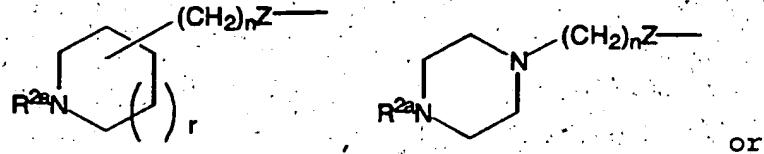


or a pharmaceutically acceptable salt form thereof
wherein:

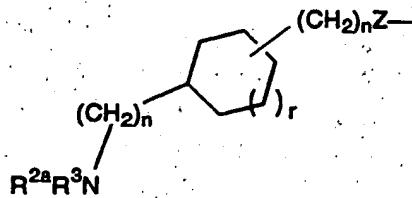
b is a single or double bond;

15

R¹ is selected from R^{2a}(R³)N-, R²(R³)N(R²N=)C-,
R^{2a}(R³)N(CH₂)_qZ-, R²(R³)N(R²N=)C(CH₂)_qZ-,



20



Z is selected from a bond, O, S, S(=O), S(=O)₂;

25 R² and R³ are independently selected from: H, C₁-C₁₀ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, C₆-C₁₀ aryl, C₇-C₁₁ arylalkyl, C₂-C₇

346

alkylcarbonyl, C₇-C₁₁ arylcarbonyl, C₂-C₁₀
alkoxycarbonyl, C₄-C₁₁ cycloalkoxycarbonyl, C₇-C₁₁
bicycloalkoxycarbonyl, C₇-C₁₁ aryloxycarbonyl,
aryl(C₁-C₁₀ alkoxy)carbonyl,
5 alkylcarbonyloxyalkoxycarbonyl, or
alkoxycarbonyloxyalkoxycarbonyl, C₁-C₆
alkylcarbonyloxy(C₁-C₄ alkoxy)carbonyl, C₆-C₁₀
arylcarbonyloxy(C₁-C₄ alkoxy)carbonyl, C₄-C₁₁
cycloalkylcarbonyloxy(C₁-C₄ alkoxy)carbonyl;

10

R^{2a} is R² or R²(R³)N(R²N=)C;

U is selected from:

a single bond,
15 - (C₁-C₇ alkyl)-,
- (C₂-C₇ alkenyl)-,
- (C₂-C₇ alkynyl)-,
- (aryl)- substituted with 0-3 R^{6a}, or
- (pyridyl)- substituted with 0-3 R^{6a};

20

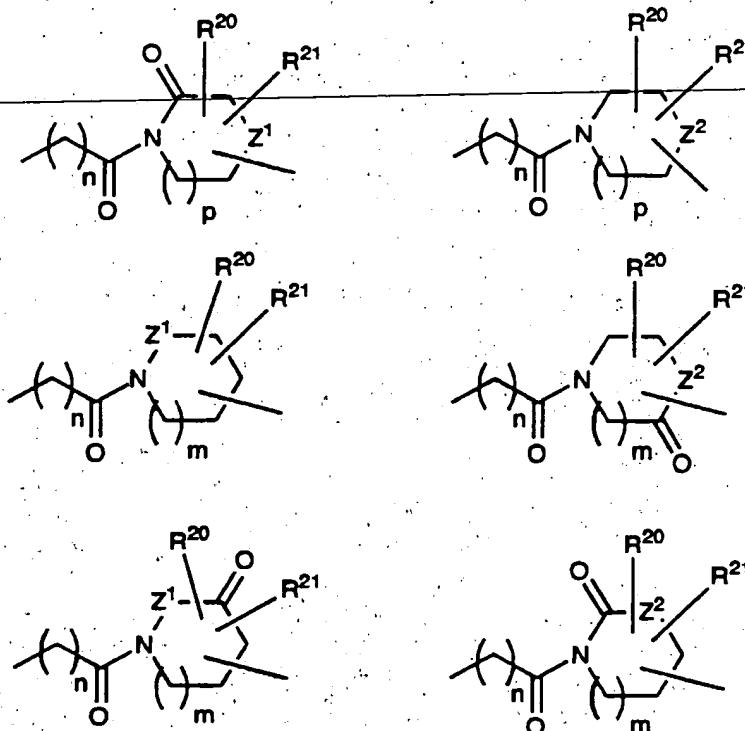
V is selected from:

a single bond;
- (C₁-C₇ alkyl)-, substituted with 0-3 groups
independently selected from R⁶ or R⁷;
25 - (C₂-C₇ alkenyl)-, substituted with 0-3 groups
independently selected from R⁶ or R⁷;
- (C₂-C₇ alkynyl)-, substituted with 0-3 groups
independently selected from R⁶ or R⁷;
- (phenyl)-, substituted with 0-2 groups
30 independently selected from R⁶ or R⁷;
- (pyridyl)-, substituted with 0-2 groups
independently selected from R⁶ or R⁷;
- (pyridazinyl)-, substituted with 0-2 groups
independently selected from R⁶ or R⁷;

35

347

W is selected from:



X is selected from:

5 a single bond,

- (C(R⁴))_n - C(R⁴) (R⁸) - C(R⁴) (R^{4a}) -

with the proviso that when n is 0 or 1, then at least one of R<sup>4a</sup> or R<sup>8</sup> is other than H or methyl;

10 Y selected from:

hydroxy,

C₁ to C₁₀ alkyloxy,C₃ to C₁₁ cycloalkyloxy,C₆ to C₁₀ aryloxy,15 C₇ to C₁₁ aralkyloxy,C₃ to C₁₀ alkylcarbonyloxyalkyloxy,C₃ to C₁₀ alkoxy carbonyloxyalkyloxy,C₂ to C₁₀ alkoxy carbonylalkyloxy,C₅ to C₁₀ cycloalkylcarbonyloxyalkyloxy,20 C₅ to C₁₀ cycloalkoxycarbonyloxyalkyloxy,

348

C₅ to C₁₀ cycloalkoxycarbonylalkyloxy,C₇ to C₁₁ aryloxycarbonylalkyloxy,C₈ to C₁₂ aryloxycarbonyloxyalkyloxy,C₈ to C₁₂ arylcarbonyloxyalkyloxy,C₅ to C₁₀ alkoxyalkylcarbonyloxyalkyloxy,C₅ to C₁₀ (5-alkyl-1,3-dioxa-cyclopenten-2-one-
y1)methoxy,C₁₀ to C₁₄ (5-aryl-1,3-dioxa-cyclopenten-2-one-
y1)methoxy,10. (R²)(R³)N-(C₁-C₁₀ alkoxy)-;z¹ is -C-, -O-, or -NR²²-;z² is -O-, or -NR²²-;15. R⁴ is selected from H, C₁-C₁₀ alkyl, C₁-C₁₀
alkylcarbonyl, aryl, arylalkylene cycloalkyl, or
cycloalkylalkylene;20. alternately, two R⁴ groups on adjacent carbon atoms may
join to form a bond, thereby to form a carbon-
carbon double or triple bond between such adjacent
carbon atoms;25. R^{4a} is selected from H, hydroxy, C₁-C₁₀ alkoxy, nitro,
N(R⁵)R^{5a}, -N(R¹²)R¹³, -N(R¹⁶)R¹⁷,
C₁-C₁₀ alkyl substituted with 0-3 R⁶,
aryl substituted with 0-3 R⁶, or
C₁-C₁₀ alkylcarbonyl;30. R^{4b} is selected from H, C₁-C₆ alkyl, C₂-C₆ alkenyl,
C₂-C₆ alkynyl, hydroxy, C₁-C₆ alkoxy, C₁-C₆
alkylthio, C₁-C₆ alkylsulfinyl, C₁-C₆ alkylsulfonyl,
nitro, C₁-C₆ alkylcarbonyl, C₆-C₁₀ aryl, -N(R¹²)R¹³,

349

halo, CF₃, CN, C₁-C₆ alkoxy carbonyl, carboxy, piperidinyl, or pyridyl;

5 R⁵ is selected from H, C₁-C₈ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylmethyl, C₆-C₁₀ aryl, C₇-C₁₁ arylalkyl, or C₁-C₁₀ alkyl substituted with 0-2 R^{4b};

10 R^{5a} is selected from hydrogen, hydroxy, C₁ to C₈ alkyl, C₂ to C₆ alkenyl, C₃ to C₁₁ cycloalkyl, C₄ to C₁₁ cycloalkylmethyl, C₁-C₆ alkoxy, benzyloxy, C₆ to C₁₀ aryl, heteroaryl, C₇ to C₁₁ arylalkyl, or C₁-C₁₀ alkyl substituted with 0-2 R^{4b};

15 alternately, R⁵ and R^{5a} when both are substituents on the same nitrogen atom (as in -NR⁵R^{5a}) can be taken together with the nitrogen atom to which they are attached to form 3-azabicyclononyl, 1,2,3,4-tetrahydro-1-isoquinolinyl, 1-piperidinyl, 1-morpholinyl, 1-pyrrolidinyl, thiamorpholinyl, thiazolidinyl or 1-piperazinyl, each being optionally substituted with C₁-C₆ alkyl, C₆-C₁₀ aryl, heteroaryl, C₇-C₁₁ arylalkyl, C₁-C₆ alkylcarbonyl, C₃-C₇ cycloalkylcarbonyl, C₁-C₆ alkoxy carbonyl, C₇-C₁₁ arylalkoxycarbonyl, C₁-C₆ alkylsulfonyl or C₆-C₁₀ arylsulfonyl;

30 R^{5b} is selected from C₁-C₈ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylmethyl, C₆-C₁₀ aryl, C₇-C₁₁ arylalkyl, or C₁-C₁₀ alkyl substituted with 0-2 R^{4b};

35 R⁶ is selected from H, C₁-C₁₀ alkyl, hydroxy, C₁-C₁₀ alkoxy, nitro, C₁-C₁₀ alkylcarbonyl, -N(R¹²)R¹³,

350

5 cyano, halo, CF_3 , CHO , CO_2R^5 , $\text{C}(=\text{O})\text{R}^{5a}$, $\text{CONR}^{5a}\text{R}^{5a}$,
 $\text{OC}(=\text{O})\text{R}^{5a}$, $\text{OC}(=\text{O})\text{OR}^{5b}$, OR^5 , $\text{OC}(=\text{O})\text{NR}^{5a}\text{R}^{5a}$, $\text{OCH}_2\text{CO}_2\text{R}^5$,
 $\text{CO}_2\text{CH}_2\text{CO}_2\text{R}^5$, NO_2 , $\text{NR}^{5a}\text{C}(=\text{O})\text{R}^{5a}$, $\text{NR}^{5a}\text{C}(=\text{O})\text{OR}^{5b}$,
 $\text{NR}^{5a}\text{C}(=\text{O})\text{NR}^{5a}\text{R}^{5a}$, $\text{NR}^{5a}\text{SO}_2\text{NR}^{5a}\text{R}^{5a}$, $\text{NR}^{5a}\text{SO}_2\text{R}^5$, $\text{S(O)}_m\text{R}^5$,
 $\text{SO}_2\text{NR}^{5a}\text{R}^{5a}$, C_2 to C_6 alkenyl, C_3 to C_{11} cycloalkyl,
 C_4 to C_{11} cycloalkylmethyl;

10 C_6 to C_{10} aryl optionally substituted with 1-3
groups selected from halogen, C_1 - C_6 alkoxy, C_1 - C_6
alkyl, CF_3 , $\text{S(O)}_m\text{Me}$, or $-\text{NMe}_2$;

15 C_7 to C_{11} arylalkyl, said aryl being optionally
substituted with 1-3 groups selected from halogen,
 C_1 - C_6 alkoxy, C_1 - C_6 alkyl, CF_3 , $\text{S(O)}_m\text{Me}$, or $-\text{NMe}_2$;

20 15 methylenedioxy when R^6 is a substituent on aryl; or
a 5-6 membered heterocyclic ring containing 1-2 N,
O, or S heteroatoms, wherein said heterocyclic
ring may be saturated, partially saturated, or
fully unsaturated, said heterocyclic ring
being substituted with 0-2 R^7 ;

25 R^{6a} is selected from C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halo,

25 CF_3 , NO_2 , or $\text{NR}^{12}\text{R}^{13}$;

30 R^7 is selected from H, C_1 - C_{10} alkyl, hydroxy, C_1 - C_{10}
alkoxy, nitro, C_1 - C_{10} alkylcarbonyl, $-\text{N}(\text{R}^{12})\text{R}^{13}$,
cyano, halo, CF_3 , CHO , CO_2R^5 , $\text{C}(=\text{O})\text{R}^{5a}$, $\text{CONR}^{5a}\text{R}^{5a}$,
 $\text{OC}(=\text{O})\text{R}^{5a}$, $\text{OC}(=\text{O})\text{OR}^{5b}$, OR^{5a} , $\text{OC}(=\text{O})\text{NR}^{5a}\text{R}^{5a}$, $\text{OCH}_2\text{CO}_2\text{R}^5$,
 $\text{CO}_2\text{CH}_2\text{CO}_2\text{R}^5$, NO_2 , $\text{NR}^{5a}\text{C}(=\text{O})\text{R}^{5a}$, $\text{NR}^{5a}\text{C}(=\text{O})\text{OR}^{5b}$,
 $\text{NR}^{5a}\text{C}(=\text{O})\text{NR}^{5a}\text{R}^{5a}$, $\text{NR}^{5a}\text{SO}_2\text{NR}^{5a}\text{R}^{5a}$, $\text{NR}^{5a}\text{SO}_2\text{R}^5$, $\text{S(O)}_m\text{R}^{5a}$,
 $\text{SO}_2\text{NR}^{5a}\text{R}^{5a}$, C_2 to C_6 alkenyl, C_3 to C_{11} cycloalkyl,
 C_4 to C_{11} cycloalkylmethyl, C_6 to C_{10} aryl, or C_7 to
 C_{11} arylalkyl;

R⁸ is selected from:

R⁶;

C₂-C₁₀ alkyl, substituted with 0-3 R⁶;

5 C₂-C₁₀ alkenyl, substituted with 0-3 R⁶;

C₂-C₁₀ alkynyl, substituted with 0-3 R⁶;

C₃-C₈ cycloalkyl, substituted with 0-3 R⁶;

C₅-C₆ cycloalkenyl, substituted with 0-3 R⁶;

aryl, substituted with 0-3 R⁶;

10 5-6 membered heterocyclic ring containing 1-2 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-2 R⁶;

15

R¹² and R¹³ are independently H, C₁-C₁₀ alkyl, C₁-C₁₀

alkoxycarbonyl, C₁-C₁₀ alkylcarbonyl, C₁-C₁₀

alkylsulfonyl, aryl(C₁-C₁₀ alkyl)sulfonyl,

arylsulfonyl, aryl, C₂-C₆ alkenyl, C₃-C₁₁

20 cycloalkyl, C₄-C₁₁ cycloalkylalkyl, C₇-C₁₁ arylalkyl, C₇-C₁₁ arylcarbonyl, C₄-C₁₁ cycloalkoxycarbonyl, C₇-C₁₁ bicycloalkoxycarbonyl, C₇-C₁₁ aryloxycarbonyl, or aryl(C₁-C₁₀ alkoxy)carbonyl, wherein said aryls are optionally substituted with 0-3 substituents

25 selected from the group consisting of: C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, CF₃, and NO₂;

R¹⁴ is selected from H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl,

C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, aryl, heteroaryl or

30 C₁-C₁₀ alkoxycarbonyl, CO₂R⁵ or -C(=O)N(R⁵)R^{5a};

R¹⁵ is selected from:

H;

R⁶;

35 C₁-C₁₀ alkyl, substituted with 0-3 R⁶;

C₂-C₁₀ alkenyl, substituted with 0-3 R⁶;

5 C₁-C₁₀ alkoxy, substituted with 0-3 R⁶;
 aryl, substituted with 0-3 R⁶;
 10 5-6 membered heterocyclic ring containing 1-2 N, O,
 or S heteroatoms, wherein said heterocyclic
 ring may be saturated, partially saturated, or
 fully unsaturated, said heterocyclic ring
 being substituted with 0-2 R⁶;

C₁-C₁₀ alkoxy carbonyl substituted with 0-2 R⁶;

-CO₂R⁵; or

15 -C(=O)N(R¹²)R¹³;

provided that when b is a double bond, only one of R¹⁴
 or R¹⁵ is present;

R¹⁶ is selected from:

15 -C(=O)-O-R^{18a},

-C(=O)-R^{18b},

-C(=O)N(R^{18b})₂,

-C(=O)NHSO₂R^{18a},

-C(=O)NHC(=O)R^{18b},

20 -C(=O)NHC(=O)OR^{18a},

-C(=O)NHSO₂NHR^{18b},

-C(=S)-NH-R^{18b},

-NH-C(=O)-O-R^{18a},

-NH-C(=O)-R^{18b},

25 -NH-C(=O)-NH-R^{18b},

-SO₂-O-R^{18a},

-SO₂-R^{18a},

-SO₂-N(R^{18b})₂,

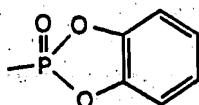
-SO₂-NHC(=O)O^{18b},

30 -P(=S)(OR^{18a})₂,

-P(=O)(OR^{18a})₂,

-P(=S)(R^{18a})₂,

-P(=O)(R^{18a})₂, or



R¹⁷ is selected from: H, C₁-C₁₀ alkyl, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₅ cycloalkylalkyl, aryl, aryl(C₁-C₁₀ alkyl)-;

5

R^{18a} is selected from:

C₁-C₈ alkyl substituted with 0-2 R¹⁹,
C₂-C₈ alkenyl substituted with 0-2 R¹⁹,
C₂-C₈ alkynyl substituted with 0-2 R¹⁹,
10 C₃-C₈ cycloalkyl substituted with 0-2 R¹⁹,
aryl substituted with 0-4 R¹⁹,
aryl(C₁-C₆ alkyl)- substituted with 0-4 R¹⁹,

15 a 5-10 membered heterocyclic ring system having 1-3 heteroatoms selected independently from O, S, and N, said heterocyclic ring being substituted with 0-4 R¹⁹,

20 C₁-C₆ alkyl substituted with a 5-10 membered heterocyclic ring system having 1-3 heteroatoms selected independently from O, S, and N, said heterocyclic ring being substituted with 0-4 R¹⁹;

25 R^{18b} is selected from R^{18a} or H;

30 R¹⁹ is selected from H, halogen, CF₃, CN, NO₂, NR¹²R¹³, C₁-C₈ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylalkyl, aryl, aryl(C₁-C₆ alkyl)-, C₁-C₆ alkoxy, or C₁-C₄ alkoxycarbonyl;

35 R²⁰ and R²¹ are each independently selected from H, C₁-C₁₀ alkyl, CO₂R⁵, C(=O)R^{5a}, CONR⁵R^{5a}, NR⁵C(=O)R^{5a}, NR¹²R¹³, C₂-C₆ alkenyl, C₃-C₁₁ cycloalkyl, C₄-C₁₁ cycloalkylmethyl, C₆-C₁₀ aryl, or C₇-C₁₁ arylalkyl;

35

R^{22} is selected from C_1-C_{10} alkyl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{15} cycloalkylalkyl, aryl, aryl(C_1-C_{10} alkyl)-; $C(=O)R^{5a}$, CO_2R^{5b} , $-C(=O)N(R^5)R^{5a}$, or a bond to X ;

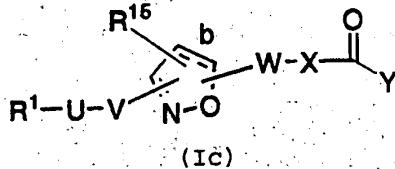
5

 m is 0-2; n is 0-2; p is 1-2; q is 1-7;10 r is 0-3;

provided that n , q and r are chosen such that the number of atoms connecting R^1 and Y is in the range of 8-17.

15

25. A compound of Claim 24 of Formula Ic:



20 wherein:

 Z is selected from a bond, O, or S;

R^2 is selected from H, aryl(C_1-C_{10} alkoxy)carbonyl, or C_1-C_{10} alkoxycarbonyl;

25

 U is a single bond; X is $-CHR^{4a}-$;

30 R^5 is selected from H or C_1-C_{10} alkyl substituted with 0-6 R^{4b} ;

R⁶ and R⁷ are each independently selected from H, C₁-C₁₀ alkyl, hydroxy, C₁-C₁₀ alkoxy, nitro, C₁-C₁₀ alkylcarbonyl, -N(R¹²)R¹³, cyano, or halo;

5 R¹² and R¹³ are each independently selected from H, C₁-C₁₀ alkyl, C₁-C₁₀ alkoxy carbonyl, C₁-C₁₀ alkylcarbonyl, C₁-C₁₀ alkylsulfonyl, aryl(C₁-C₁₀ alkyl)sulfonyl, arylsulfonyl, or aryl, wherein said aryls are optionally substituted with 10 0-3 substituents selected from the group consisting of: C₁-C₄ alkyl, C₁-C₄ alkoxy, halo, CF₃, and NO₂;

15 R¹⁵ is selected from H, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, aryl, heteroaryl or C₁-C₁₀ alkoxy carbonyl, CO₂R⁵ or -C(=O)N(R⁵)R^{5a};

20 R¹⁶ is selected from:
-C(=O)-O-R^{18a},
-C(=O)-R^{18b},
-S(=O)₂-R^{18a};

R¹⁷ is selected from: H or C₁-C₄ alkyl;

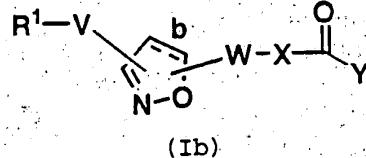
25 R^{18a} is selected from:
C₁-C₈ alkyl substituted with 0-2 R¹⁹,
C₂-C₈ alkenyl substituted with 0-2 R¹⁹,
C₂-C₈ alkynyl substituted with 0-2 R¹⁹,
C₃-C₈ cycloalkyl substituted with 0-2 R¹⁹,
aryl substituted with 0-2 R¹⁹,
30 aryl(C₁-C₆ alkyl) - substituted with 0-2 R¹⁹,

35 a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, triazolyl, imidazolyl, benzofuranyl, indolyl, indolinyl, quinolinyl, isoquinolinyl, isoxazolinyl,

benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3H-indolyl, carbazolyl, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-2 R¹⁹;

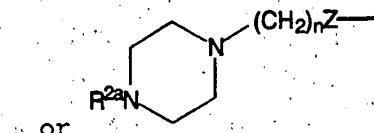
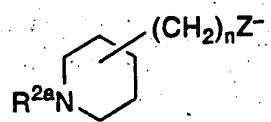
5 C₁-C₆ alkyl substituted with a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolinyl, benzofuranyl, indolyl, indolanyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3H-indolyl, indolyl, carbazole, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-2 R¹⁹.

26. A compound of Claim 24 of Formula Ib:



wherein:

25 R¹ is selected from: R²(R³)N-, R²NH(R²N=)C-, R²R³N(CH₂)_pZ-, R²NH(R²N=)CNH(CH₂)_pZ-,



30 n is 0-1;

p is 2-4;

p" is 4-6;

Z is selected from a bond or O;

5 R³ is H or C₁-C₅ alkyl;

V is a single bond, or
-(phenyl)-;

10 X is selected from:

-CH₂-,
-CHN(R¹⁶)R¹⁷-, or
-CHNR⁵R^{5a}-;

15 Y is selected from:

hydroxy;
C₁ to C₁₀ alkoxy;
methylcarbonyloxymethoxy-;

20 t-butyloxycarbonyloxymethoxy-;

cyclohexylcarbonyloxymethoxy-;

1-(methylcarbonyloxy)ethoxy-;

1-(ethylcarbonyloxy)ethoxy-;

1-(t-butyloxycarbonyloxy)ethoxy-;

25 1-(cyclohexylcarbonyloxy)ethoxy-;

i-propyloxycarbonyloxymethoxy-;

t-butyloxycarbonyloxymethoxy-;

1-(i-propyloxycarbonyloxy)ethoxy-;

1-(cyclohexyloxycarbonyloxy)ethoxy-;

30 1-(t-butyloxycarbonyloxy)ethoxy-;

dimethylaminoethoxy-;

diethylaminoethoxy-;

(5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;

(5-(t-butyl)-1,3-dioxacyclopenten-2-on-4-

35 yl)methoxy-;

(1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methoxy-;

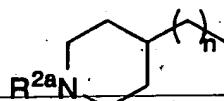
358

1- (2- (2-methoxypropyl)carbonyloxy)ethoxy-;

R^{18a} is selected from:C₁-C₄ alkyl substituted with 0-2 R¹⁹,5 C₂-C₄ alkenyl substituted with 0-2 R¹⁹,C₂-C₄ alkynyl substituted with 0-2 R¹⁹,C₃-C₄ cycloalkyl substituted with 0-2 R¹⁹,aryl substituted with 0-2 R¹⁹,10 aryl(C₁-C₄ alkyl)- substituted with 0-2 R¹⁹,15 a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, triazolyl, imidazolyl, benzofuranyl, indolyl, indolinyl, quinolinyl, isoquinolinyl, isoxazolinyl, benzimidazolyl, piperidinyl, tetrahydrofuran, 15 pyran, pyridinyl, 3H-indolyl, carbazolyl, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-2 R¹⁹;20 C₁-C₆ alkyl substituted with a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolinyl, benzofuranyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, 25 piperidinyl, tetrahydrofuran, pyran, pyridinyl, 3H-indolyl, indolyl, carbazole, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-2 R¹⁹.

30 27. A compound of Claim 26 wherein:

R¹ is R²NH(R²N=)C- or R²NH(R²N=)CNH- and V is phenyl or pyridyl; or35 R¹ is



, and V is a single bond;

n is 1-2;

5

R³ is H or C₁-C₅ alkyl;

10

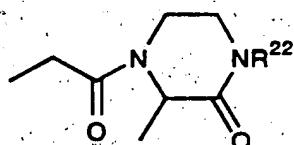
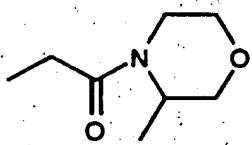
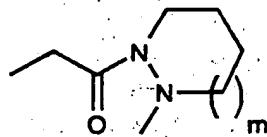
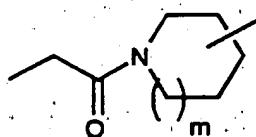
X is selected from:

-CH₂-,

-CHN(R¹⁶)R¹⁷-; or

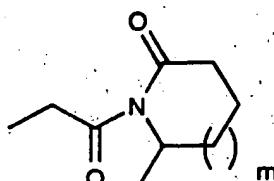
-CHNR⁵R^{5a}-;

W is selected from:



15

or



m is 1-3;

Y is selected from:

hydroxy; 360
C₁ to C₁₀ alkoxy;
methylcarbonyloxymethoxy-;
ethylcarbonyloxymethoxy-;
5 t-butylcarbonyloxymethoxy-;
cyclohexylcarbonyloxymethoxy-;
1-(methylcarbonyloxy)ethoxy-;
1-(ethylcarbonyloxy)ethoxy-;
1-(t-butylcarbonyloxy)ethoxy-;
10 1-(cyclohexylcarbonyloxy)ethoxy-;
i-propyloxycarbonyloxymethoxy-;
t-butyloxycarbonyloxymethoxy-;
1-(i-propyloxycarbonyloxy)ethoxy-;
1-(cyclohexyloxycarbonyloxy)ethoxy-;
15 1-(t-butyloxycarbonyloxy)ethoxy-;
dimethylaminoethoxy-;
diethylaminoethoxy-;
(5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;
(5-(t-butyl)-1,3-dioxacyclopenten-2-on-4-
20 yl)methoxy-;
(1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methoxy-;
1-(2-(2-methoxypropyl)carbonyloxy)ethoxy-;

R¹⁹ is H, halogen, C₁-C₄ alkyl, C₃-C₇ cycloalkyl,
25 cyclopropylmethyl, aryl, or benzyl;

R²⁰ and R²¹ are both H;

R²² is H, C₁-C₄ alkyl or benzyl.

30

28. A compound of Claim 24, or a pharmaceutically acceptable salt form thereof, selected from:

2-(R,S)-2-carboxymethyl-1-[5-(R,S)-N-[3-(4-
35 amidinophenyl)isoxazolin-5-yl acetyl]piperidine;

2- (R,S) -2-carboxymethyl-1-[5-(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-yl acetyl]azepine;

2- (R,S) -2-carboxymethyl-1-[5-(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-yl acetyl]pyrrolidine;

5 3- (R,S) -carboxymethyl-4-[5-(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-yl acetyl]piperazine-2-one;

6- (R,S) -carboxymethyl-1-[5-(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-yl acetyl]piperidine-2-one;

10 5- (R,S) -carboxymethyl-1-[5-(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-yl acetyl]pyrrolidine-2-one;

7- (R,S) -carboxymethyl-1-[5-(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-yl acetyl]azetidine-2-one;

15 2- (R,S) -carboxymethyl-1-[5-(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-yl acetyl]pyrazolidine;

3- (R,S) -carboxymethyl-4-[5-(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-yl acetyl]morpholine.

29. A method for the prevention or treatment of thrombosis which comprises administering to a host in need of such treatment a therapeutically effective amount of a compound of Claim 1, 6, 11, 16, 20, or 24.

30. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1, 6, 11, 16, 20, or 24 and a pharmaceutically acceptable carrier.

31. A method of inhibiting the aggregation of blood platelets which comprises administering to a host in need of such inhibition a therapeutically effective amount of a compound of Claim 1, 6, 11, 16, 20, or 24.

362

32. A method of treating thromboembolic disorders selected from thrombus or embolus formation, harmful platelet aggregation, reocclusion following thrombolysis, reperfusion injury, restenosis, 5 atherosclerosis, stroke, myocardial infarction, and unstable angina, which comprises administering to a host in need of such treatment a therapeutically effective amount of a compound of Claim 6.

10 33. A method for the treatment of thrombosis which comprises administering to a host in need of such treatment a therapeutically effective amount of a compound of Claim 6 in combination with one or more additional therapeutic agents selected from: a 15 thromolytic agent, an anti-coagulant agent, or an anti-platelet agent.

34. A method of treating rheumatoid arthritis, asthma, allergies, adult respiratory syndrome, organ 20 transplantation rejection, septic shock, psoriasis, contact dermatitis, osteoporosis, osteoarthritis, tumor metastasis, diabetic retinopathy, inflammatory conditions and inflammatory bowel disease, comprising administering to a host in need of such treatment a 25 therapeutically effective amount of a compound of Claim 6.

AMENDED CLAIMS

[received by the International Bureau on 29 March 1995 (29.03.95);
new claims 35-38 added; (8. pages)]

35. A compound of Claim 6, or enantiomeric or
diasteriometric forms thereof, or mixtures of
enantiomeric or diasteriometric forms thereof, or a
pharmaceutically acceptable salt form thereof, selected
5 from:

N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²- (phenylsulfonyl)-2,3-diaminopropanoic acid;
N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
10 N²- (4-methyl-phenyl-sulfonyl)-2,3-diaminopropanoic
acid;
N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²- (butanesulfonyl)-2,3-diaminopropanoic acid;
N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
15 N²- (propanesulfonyl)-2,3-diaminopropanoic acid;
N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²- (ethanesulfonyl)-2,3-diaminopropanoic acid;
N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²- (methyloxycarbonyl)-2,3-diaminopropanoic acid;
20 N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²- (ethyloxycarbonyl)-2,3-diaminopropanoic acid;
N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²- (1-propyloxycarbonyl)-2,3-diaminopropanoic acid;
N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
25 N²- (2-propyloxycarbonyl)-2,3-diaminopropanoic acid;
N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²- (n-butyloxycarbonyl)-2,3-diaminopropanoic acid;
N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²- (1-(2-methyl)-propyloxycarbonyl)-2,3-
30 diaminopropanoic acid;
N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²- (2-(2-methyl)-propyloxycarbonyl)-2,3-
diaminopropanoic acid;
N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
35 N²- (benzyloxycarbonyl)-2,3-diaminopropanoic acid;

364

N³ - [2 - {3 - (4 - formamidinophenyl) - isoxazolin - 5 - yl} - acetyl] -
N² - (4 - methylbenzyloxycarbonyl) - 2,3 - diaminopropanoic
acid;

5 N³ - [2 - {3 - (4 - formamidinophenyl) - isoxazolin - 5 - yl} - acetyl] -
N² - (4 - methoxybenzyloxycarbonyl) - 2,3 -
diaminopropanoic acid;

10 N³ - [2 - {3 - (4 - formamidinophenyl) - isoxazolin - 5 - yl} - acetyl] -
N² - (4 - chlorobenzyloxycarbonyl) - 2,3 - diaminopropanoic
acid;

15 N³ - [2 - {3 - (4 - formamidinophenyl) - isoxazolin - 5 - yl} - acetyl] -
N² - (4 - fluorobenzyloxycarbonyl) - 2,3 - diaminopropanoic
acid;

20 N³ - [2 - {3 - (4 - formamidinophenyl) - isoxazolin - 5 - yl} - acetyl] -
N² - (2 - (methyloxyethyl) - oxycarbonyl) - 2,3 -
diaminopropanoic acid;

25 N³ - [2 - {3 - (4 - formamidinophenyl) - isoxazolin - 5 - yl} - acetyl] -
N² - (2 - pyridinylcarbonyl) - 2,3 - diaminopropanoic acid;

30 N³ - [2 - {3 - (4 - formamidinophenyl) - isoxazolin - 5 - yl} - acetyl] -
N² - (3 - pyridinylcarbonyl) - 2,3 - diaminopropanoic
acid;

N³ - [2 - {3 - (4 - formamidinophenyl) - isoxazolin - 5 - yl} - acetyl] -
N² - (4 - pyridinyl - carbonyl) - 2,3 - diaminopropanoic
acid;

N³ - [2 - {3 - (4 - formamidinophenyl) - isoxazolin - 5 - yl} - acetyl] -
N² - (2 - (2 - pyridinyl) - acetyl) - 2,3 - diaminopropanoic
acid;

N³ - [2 - {3 - (4 - formamidinophenyl) - isoxazolin - 5 - yl} - acetyl] -
N² - (2 - (3 - pyridinyl) - acetyl) - 2,3 - diaminopropanoic
acid;

N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²-(2-(4-pyridinyl)-acetyl)-2,3-diaminopropanoic
acid;

5 N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²-(2-pyridyl-methyloxycarbonyl)-2,3-
diaminopropanoic acid;

N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²-(3-pyridyl-methyloxycarbonyl)-2,3-
diaminopropanoic acid;

10 N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²-(4-pyridyl-methyloxycarbonyl)-2,3-
diaminopropanoic acid;

N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²-(4-butyloxyphenylsulfonyl)-2,3-diaminopropanoic
15 acid;

N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²-(2-thienylsulfonyl)-2,3-diaminopropanoic acid;

N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²-(3-methylphenylsulfonyl)-2,3-diaminopropanoic
20 acid;

N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²-(4-iodophenylsulfonyl)-2,3-diaminopropanoic
acid;

N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
25 N²-(3-trifluoromethylphenylsulfonyl)-2,3-
diaminopropanoic acid;

N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²-(3-chlorophenylsulfonyl)-2,3-diaminopropanoic
acid;

30 N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²-(3-2-methoxycarbonylphenylsulfonyl)-2,3-
diaminopropanoic acid;

N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²-(2,4,6-trimethylphenylsulfonyl)-2,3-
35 diaminopropanoic acid;

1 N³ - [2 - {3 - (4 - formamidinophenyl) - isoxazolin - 5 - yl} - acetyl] -
2 N² - (2 - chlorophenylsulfonyl) - 2,3 - diaminopropanoic
acid;

5 N³ - [2 - {3 - (4 - formamidinophenyl) - isoxazolin - 5 - yl} - acetyl] -
6 N² - (4 - trifluoromethylphenylsulfonyl) - 2,3 -
diaminopropanoic acid;

10 N³ - [2 - {3 - (4 - formamidinophenyl) - isoxazolin - 5 - yl} - acetyl] -
11 N² - (2 - trifluoromethylphenylsulfonyl) - 2,3 -
diaminopropanoic acid;

15 N³ - [2 - {3 - (4 - formamidinophenyl) - isoxazolin - 5 - yl} - acetyl] -
16 N² - (2 - fluorophenylsulfonyl) - 2,3 - diaminopropanoic
acid;

20 N³ - [2 - {3 - (4 - formamidinophenyl) - isoxazolin - 5 - yl} - acetyl] -
21 N² - (4 - fluorophenylsulfonyl) - 2,3 - diaminopropanoic
acid;

25 N³ - [2 - {3 - (4 - formamidinophenyl) - isoxazolin - 5 - yl} - acetyl] -
26 N² - (4 - methoxyphenylsulfonyl) - 2,3 - diaminopropanoic
acid;

30 N³ - [2 - {3 - (4 - formamidinophenyl) - isoxazolin - 5 - yl} - acetyl] -
31 N² - (2,3,5,6 - tetramethylphenylsulfonyl) - 2,3 -
diaminopropanoic acid;

35 N³ - [2 - {3 - (4 - formamidinophenyl) - isoxazolin - 5 - yl} - acetyl] -
36 N² - (4 - cyanophenylsulfonyl) - 2,3 - diaminopropanoic
acid;

40 N³ - [2 - {3 - (4 - formamidinophenyl) - isoxazolin - 5 - yl} - acetyl] -
41 N² - (4 - chlorophenylsulfonyl) - 2,3 - diaminopropanoic
acid;

45 N³ - [2 - {3 - (4 - formamidinophenyl) - isoxazolin - 5 - yl} - acetyl] -
46 N² - (4 - propylphenylsulfonyl) - 2,3 - diaminopropanoic
acid;

50 N³ - [2 - {3 - (4 - formamidinophenyl) - isoxazolin - 5 - yl} - acetyl] -
51 N² - (2 - phenylethylsulfonyl) - 2,3 - diaminopropanoic
acid;

55 N³ - [2 - {3 - (4 - formamidinophenyl) - isoxazolin - 5 - yl} - acetyl] -
56 N² - (4 - isopropylphenylsulfonyl) - 2,3 - diaminopropanoic
acid;

N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²-(3-phenylpropylsulfonyl)-2,3-diaminopropanoic
acid;

5 N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²-(3-pyridylsulfonyl)-2,3-diaminopropanoic acid;

N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²-(phenylaminosulfonyl)-2,3-diaminopropanoic acid;

N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²-(benzylaminosulfonyl)-2,3-diaminopropanoic acid;

10 N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²-(dimethylaminosulfonyl)-2,3-diaminopropanoic
acid;

N³-[2-(3-(2-fluoro-4-formamidinophenyl)-isoxazolin-5-
yl)-acetyl]-N²-(3-methylphenylsulfonyl)-2,3-
15 diaminopropanoic acid;

N³-[2-(3-(2-formamidino-5-pyridinyl)-isoxazolin-5-yl)-
acetyl]-N²-(n-butyloxycarbonyl)-2,3-
diaminopropanoic acid;

N³-[2-(3-(2-formamidino-5-pyridinyl)-isoxazolin-5-yl)-
20 acetyl]-N²-(3-methylphenylsulfonyl)-2,3-
diaminopropanoic acid;

N³-[2-(3-(3-formamidino-6-pyridinyl)-isoxazolin-5-yl)-
acetyl]-N²-(n-butyloxycarbonyl)-2,3-
diaminopropanoic acid;

25 N³-[2-(3-(3-formamidino-6-pyridinyl)-isoxazolin-5-yl)-
acetyl]-N²-(3-methylphenylsulfonyl)-2,3-
diaminopropanoic acid;

N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²-(phenylaminocarbonyl)-2,3-diaminopropanoic acid;

30 N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²-(4-fluorophenylaminocarbonyl)-2,3-
diaminopropanoic acid;

N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²-(1-naphthylaminocarbonyl)-2,3-diaminopropanoic
35 acid;

N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²-(benzylaminocarbonyl)-2,3-diaminopropanoic acid;

N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²-(3-bromo-2-thienylsulfonyl)-2,3-diaminopropanoic
5 acid;

N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²-(3-methyl-2-benzothienylsulfonyl)-2,3-
diaminopropanoic acid,

N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
10 N²-(isobutyloxycarbonyl)-2,3-diaminopropanoic acid,

N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²-(isobutyloxycarbonyl)-2,3-diaminopropanoic acid,

N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²-(isobutyloxycarbonyl)-2,3-diaminopropanoic acid,

15 N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²-(2-cyclopropylethoxycarbonyl)-2,3-
diaminopropanoic acid,

N³-[2-(3-(4-guanidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²-(n-butyloxycarbonyl)-2,3-diaminopropanoic acid;

20 N³-[2-(3-(4-guanidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²-(3-methylphenylsulfonyl)-2,3-diaminopropanoic
acid;

N³-[2-(5-(4-formamidinophenyl)-isoxazolin-3-yl)-acetyl]-
N²-(n-butyloxycarbonyl)-2,3-diaminopropanoic acid;

25 N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²-(2-bromo-phenylsulfonyl)-2,3-diaminopropionic acid;

30 N³-[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]-
N²-(2-methyl-phenylsulfonyl)-2,3-diaminopropionic acid;

N³-[2-(3-(3-formamidino-6-pyridinyl)-isoxazolin-5-yl)-
35 acetyl]-N²-(3-methylphenylsulfonyl)-2,3-diaminopropionic
acid;

N^3 -[2-(3-(2-formamidino-5-pyridinyl)-isoxazolin-5-yl)-acetyl]- N^2 -(3-methylphenylsulfonyl)-2,3-diaminopropionic acid;

5 N^3 -[2-(3-(2-fluoro-4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]- N^2 -(3-methylphenylsulfonyl)-2,3-diaminopropionic acid;

10 N^3 -[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]- N^2 -(3-bromo-phenylsulfonyl)-2,3-diaminopropionic acid;

N^3 -[2-(3-(4-formamidinophenyl)-isoxazolin-5-yl)-acetyl]- N^2 -(4-bromo-phenylsulfonyl)-2,3-diaminopropionic acid;

15 said enantiomeric and diasteriomeric forms being selected from:

(R,S), (R,S);

(R), (R,S);

(S), (R,S);

20 (R), (R);

(S), (R);

(R), (S);

(S), (S).

25 36. A compound of Claim 35, or enantiomeric or diasteriomeric forms thereof, or mixtures of enantiomeric or diasteriomeric forms thereof, or a pharmaceutically acceptable salt form thereof, said enantiomeric and diasteriomeric form being: (R), (S).

30

37. A prodrug ester of a compound of Claim 35, said ester being selected from the group consisting of:

methyl;

ethyl;

35 isopropyl;

methylcarbonyloxymethyl-;

370

ethylcarbonyloxymethyl-;
t-butylcarbonyloxymethyl-;
cyclohexylcarbonyloxymethyl-;
1-(methylcarbonyloxy)ethyl-;
5 1-(ethylcarbonyloxy)ethyl-;
1-(t-butylcarbonyloxy)ethyl-;
1-(cyclohexylcarbonyloxy)ethyl-;
i-propyloxycarbonyloxymethyl-;
cyclohexylcarbonyloxymethyl-;
10 t-butyloxycarbonyloxymethyl-;
1-(i-propyloxycarbonyloxy)ethyl-;
1-(cyclohexyloxycarbonyloxy)ethyl-;
1-(t-butyloxycarbonyloxy)ethyl-;
dimethylaminoethyl-;
15 diethylaminoethyl-;
(5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methyl-;
(5-(t-butyl)-1,3-dioxacyclopenten-2-on-
4-yl)methyl-;
(1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methyl-;
20 1-(2-(2-methoxypropyl)carbonyloxy)ethyl-.

38. A prodrug ester of a compound of Claim 36,
said ester being selected from the group consisting of:
methyl;
25 ethyl;
isopropyl.

INTERNATIONAL SEARCH REPORT

Internat. Application No
PCT/US 94/13155

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D261/04	C07D413/12	A61K31/42	C07D498/10	C07D413/06
C07D413/04	C07F9/653	C07F9/6571		

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 525 629 (DR. KARL THOMAE GMBH) 3 February 1993 cited in the application see page 23, line 57 - page 26, line 7; claims 1,2,7-10 ---	1,29-34
A	JOURNAL OF MEDICINAL CHEMISTRY, vol.35, no.23, 13 November 1992, WASHINGTON US pages 4393 - 4407 LEO ALLIG ET AL 'Low molecular weight, non-peptide fibrinogen receptor antagonists' see the whole document ---	1,29-34 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *B* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *A* document member of the same patent family

Date of the actual completion of the international search

16 January 1995

Date of mailing of the international search report

03.02.95

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Authorized officer

Henry, J

INTERNATIONAL SEARCH REPORT

Intern.	Application No
PCT/US 94/13155	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 478 328 (MERCK AND CO. INC.) 1 April 1992 cited in the application see claims ----	1,29-34
A	WO,A,93 16697 (MERCK AND CO. INC.) 2 September 1993 see claims ----	1,29-34
A	EP,A,0 512 831 (MERCK AND CO. INC.) 11 November 1992 cited in the application see claims ----	1,29-34
1		

INTERNATIONAL SEARCH REPORTIn national application No.

PCT/US 94/13155

Box I. Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

- Please see attached sheet -
2. Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II. Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

Remark - Although claims 29 and 31-34 are directed to a method of treatment of the human body the search has been carried out and based on the alleged effect of the compounds.

Reason - The definition of the substituents is too general and is only partly supported by the examples. Guided by the spirit of the application the search was carried out on the bases of the examples (cf. Art.6 Guidelines Exam. Part B Chpt III 3.6, 3.7)

Claims searched completely: 5, 10, 14, 15, 19, 23, 28

Claims searched incompletely: 1-4, 6-9, 11-13, 16-18, 20-22, 24-27

Claims not searched: 29-34

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Application No

PCT/US 94/13155

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0525629	03-02-93	DE-A-	4124942	28-01-93
		AU-B-	652064	11-08-94
		AU-A-	2056992	28-01-93
		JP-A-	5221999	31-08-93
EP-A-0478328	01-04-92	AU-B-	653360	29-09-94
		AU-A-	8478891	02-04-92
		CA-A-	2052069	28-03-92
		JP-A-	5155828	22-06-93
		US-A-	5294616	15-03-94
WO-A-9316697	02-09-93	US-A-	5227490	13-07-93
		AU-B-	3665793	13-09-93
EP-A-0512831	11-11-92	AU-B-	647618	24-03-94
		AU-A-	1611192	12-11-92
		BG-A-	98194	30-09-94
		CN-A-	1067883	13-01-93
		JP-A-	6009525	18-01-94
		NO-A-	933999	05-11-93
		WO-A-	9219595	12-11-92
		US-A-	5281585	25-01-94

